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GOLDEN STATE NATURAL PRODUCTS, INC.

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

GOLDEN STATE NATURAL PRODUCTS, INC., Plaintiff, v. TSI HEALTH SCIENCES, INC., Defendant.	Civil Action No. '13CV0337 JAH KSC **COMPLAINT FOR DECLARATORY JUDGMENT**

Plaintiff Golden State Natural Products, Inc. ("GSNP") hereby alleges as follows for its Complaint against TSI Health Sciences, Inc. ("TSI").

NATURE OF THIS ACTION

1. This is an action for a declaratory judgment that (1) GSNP has not infringed U.S. Patent No. 7,629,329 ("the '329 Patent") or U.S. Patent No. 7,671,038 ("the '038 Patent")(referred to collectively as "the Patents-in-Suit"); and (2) that GSNP has not breached a certain license agreement between GSNP and TSI, dated June 24, 2009 (referred to herein as "the License Agreement").

PARTIES

2. GSNP is a California corporation with its principal place of business at 2080 Las Palmas Drive, Carlsbad, California.

3. GSNP is informed and believes, and on that basis alleges, that Defendant TSI is a Montana corporation with its principal place of business at 305 S. 4th St. East, Missoula, Montana.

JURISDICTION AND VENUE

4. This declaratory judgment action arises under the patent laws of the United States, Title 35 of the United States Code, and under the Declaratory Judgment Act, 28 U.S.C. §2201.

5. This Court has original subject matter jurisdiction over this action for a declaration of non-infringement of the Patents-in-Suit, pursuant to 28 U.S.C. §§1331, 1338(a), 2201(a) and 2202.

6. This Court has supplemental subject matter jurisdiction over the claim for a declaration that GSNP did not breach the License Agreement, pursuant to 28 U.S.C. §1367. The claim is so related to the patent claims in the action that they form part of the same case or controversy under Article III of the United States Constitution.

7. This Court has personal jurisdiction over TSI, because TSI has had regular and systematic business contacts within this judicial district, including by making past sales and shipments of products to GSNP within this judicial district.

8. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

GENERAL ALLEGATIONS

9. The '329 Patent was issued on December 8, 2009, and is entitled "Method for Increasing Muscle Mass and Strength Though Administration of

Adenosine Triphosphate." A true and correct copy of the '329 Patent is attached as Exhibit A.

10. The '038 Patent was issued on March 2, 2010, and is entitled "Method of Therapeautic Treatments Including Human Immunodeficiency Virus (HIV) Disease and Other Conditions in a Human Host by Administering Adenine Nucleotides." A true and correct copy of the '038 Patent is attached as Exhibit B.

11. On or about June 24, 2009, GSNP and TSI entered into a written agreement entitled "Peak ATP® License and Supply Agreement" (referred to herein as "the License Agreement"). A true and correct copy of the License Agreement is attached as Exhibit C. The License Agreement granted certain licenses to GSNP if it purchased TSI's adenosine triphosphate (ATP) product. The License Agreement did not, however, obligate GSNP to purchase ATP only from TSI and did not prohibit GSNP from buying adenosine triphosphate (ATP) products from other suppliers.

12. GSNP bought some ATP from TSI, but, sometime during 2011, after TSI was unable to meet GSNP's product requirements, GSNP started buying ATP from a supplier other than TSI.

13. On December 13, 2012, TSI's counsel sent a letter to GSNP, on behalf of TSI. A true and correct copy of the December 13, 2012, letter is attached as Exhibit D. In the December 13, 2012, letter, TSI's counsel asserted that TSI is the owner of the '329 Patent and is the owner of the '038 Patent and accused GSNP of infringing "at least one of" the patents.

14. On December 27, 2012, GSNP's undersigned counsel wrote back to TSI's counsel, taking issue with TSI's accusations of patent infringement against GSNP. A true and correct copy of GSNP's counsel's December 27, 2012, letter is attached as Exhibit E.

15. On February 5, 2013, TSI's counsel wrote another letter to GSNP, on behalf of TSI. A true and correct copy of the February 5, 2013, letter is attached as Exhibit F. In Exhibit F, TSI's counsel accused GSNP of infringing both the '329 Patent and the '038 Patent.

16. Also in Exhibit F, TSI's counsel asserted that the License Agreement "requires GSNP to use only TSI's ATP and in delivery forms agreed to in advance by TSI." TSI's counsel asserted that GNP had "breached the license agreement and has been in breach of contract since it began purchasing ATP from any party other than TSI and is liable for those damages as well."

17. By virtue of the foregoing, there is a real, continuing and justiciable controversy between the parties (a) regarding GSNP's non-infringement of each of the Patents-in-Suit; and (b) regarding GSNP's alleged breach of the License Agreement.

FIRST CLAIM FOR RELIEF

(Declaration of Non-Infringement of the '329 Patent)

18. GSNP restates the allegations of Paragraphs 1-17 of this Complaint, as though fully set forth here.

19. TSI claims to be the owner of the '329 Patent.

20. TSI has accused GSNP of infringing the '329 Patent.

21. GSNP is not infringing, has not infringed, and is not liable for any infringement of any claim of the '329 Patent.

22. TSI's accusations of infringement against GSNP regarding the '329 Patent are objectively baseless.

23. GSNP is informed and believes, and on that basis alleges, that, absent a declaration of non-infringement of the '329 Patent, TSI will continue to accuse GSNP of infringing the '329 Patent and will in this way cause damage to GSNP.

24. GSNP seeks a declaration that it has not infringed the '329 Patent and that it is not otherwise liable for any infringement of the '329 Patent.

SECOND CLAIM FOR RELIEF

(Declaration of Non-Infringement of the '038 Patent)

25. GSNP restates the allegations of Paragraphs 1-17 of this Complaint, as though fully set forth here.

26. TSI claims to be the owner of the '038 Patent.

27. TSI has accused GSNP of infringing the '038 Patent.

28. GSNP is not infringing, has not infringed, and is not liable for any infringement of any claim of the '038 Patent.

29. TSI's accusations of infringement against GSNP regarding the '038 Patent are been objectively baseless.

30. GSNP is informed and believes, and on that basis alleges, that, absent a declaration of non-infringement of the '038 Patent, TSI will continue to accuse GSNP of infringing the '038 Patent and will in this way cause damage to GSNP.

31. GSNP seeks a declaration that it has not infringed the '038 Patent and that it is not otherwise liable for any infringement of the '038 Patent.

THIRD CLAIM FOR RELIEF

(Declaration That GSNP Is Not In Breach of the License Agreement)

32. GSNP restates the allegations of Paragraphs 1-17 of this Complaint, as though fully set forth here.

33. TSI has accused GSNP of breaching the parties June 24, 2009, Agreement, by "purchasing ATP from any party other than TSI."

34. The License Agreement did not obligate GSNP to buy ATP only from TSI. GSNP has not breached the License Agreement by buying product from any other supplier.

35. GSNP is informed and believes, and on that basis alleges, that, absent a declaration that GSMP did not breach the License Agreement by purchasing ATP from any party other than TSI, TSI will continue to accuse GSNP of breaching the License Agreement and will in this way cause damage to GSNP.

36. GSNP seeks a declaration that GSMP did not breach the License Agreement by purchasing ATP from any party other than TSI.

PRAYER FOR RELIEF

WHEREFORE, GSNP prays for judgment against TSI Health Sciences, Inc., as follows:

a) for entry of judgment that GSNP has not infringed the '392 Patent, directly or indirectly, and that GSNP is not liable for any infringement of the '392 Patent;

b) for entry of judgment that GSNP has not infringed the '038 Patent, directly or indirectly, and that GSNP is not liable for any infringement of the '038 Patent;

c) for entry of judgment that GSNP did not breach the License Agreement by purchasing ATP from any party other than TSI, and that GSNP is not liable for any breach of the License Agreement;

d) that the case be declared exceptional under 35 U.S.C. §285 and that GSNP be awarded its attorney's fees incurred in the patent-related portions of the action; and

e) that GSNP be awarded such other and further relief as the Court deems just and proper.

Respectfully submitted,

By: /s/ Richard A. Clegg
Richard A. Clegg
LAW OFFICE OF RICHARD CLEGG
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EXHIBIT A

US007629329B2

(12) **United States Patent**
Lee et al.

(10) **Patent No.: US 7,629,329 B2**
(45) **Date of Patent: Dec. 8, 2009**

(54) **METHOD FOR INCREASING MUSCLE MASS AND STRENGTH THROUGH ADMINISTRATION OF ADENOSINE TRIPHOSPHATE**

(75) Inventors: **Steve S. Lee**, Sandy, UT (US); **Richard B. Hynson**, Missoula, MT (US); **Joe Zhou**, Shanghai (CN)

(73) Assignee: **TSI Health Sciences, Inc.**, Missoula, MT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 499 days.

(21) Appl. No.: **11/069,746**

(22) Filed: **Feb. 28, 2005**

(65) **Prior Publication Data**

US 2005/0261238 A1 Nov. 24, 2005

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/162,143, filed on Jun. 3, 2002, now abandoned.

(60) Provisional application No. 60/549,181, filed on Mar. 2, 2004, provisional application No. 60/295,705, filed on Jun. 4, 2001.

(51) **Int. Cl.**
A01N 43/04 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/47**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(Continued)

Primary Examiner—Traviss C McIntosh, III
(74) *Attorney, Agent, or Firm*—Marshall, Gerstein & Borun LLP

(57) **ABSTRACT**

The present invention is directed to compositions having an effective amount of Adenosine Triphosphate ("ATP") sufficient to effect intracellular and extracellular concentrations of ATP in a mammal to improve anaerobic exercise capacity by increasing muscle size and/or strength and methods for using the same. Preferably, a gastric acid secretion inhibitory coating is applied to the effective amount of ATP in a manner that protects the ATP from degradation by gastric juices. ATP compositions of the present invention may be administered in nutraceutical or functional food dosage forms, including oral and non-oral delivery forms. In addition, the effective amount of ATP maybe combined with amino acids, botanicals, functional foods, herbals, nucleotides, nutraceuticals, nutrients, pharmaceuticals, proteins, and/or vitamins in an effort to enhance the targeted activity of the composition.

27 Claims, 18 Drawing Sheets

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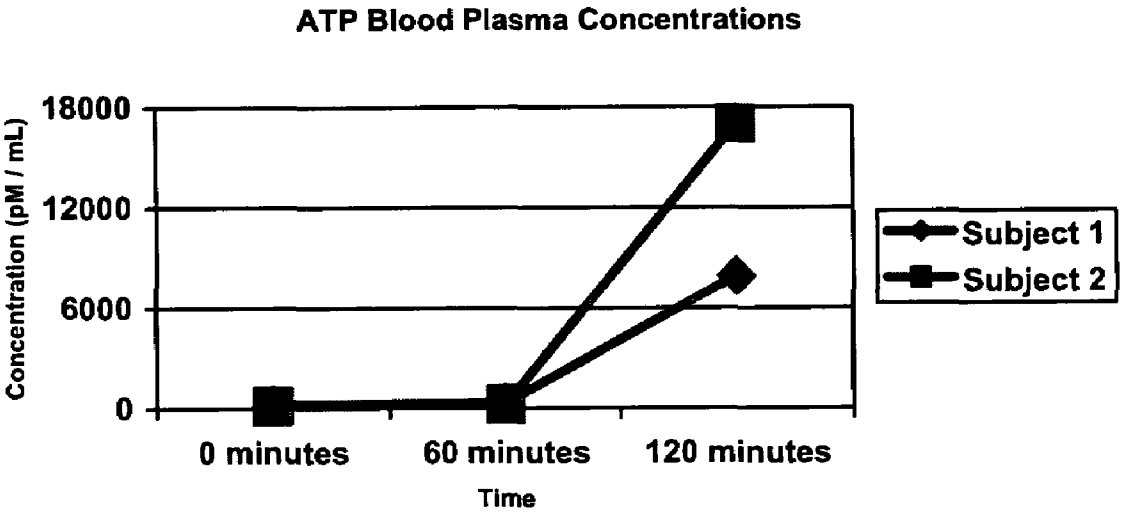

ATP Blood Plasma Concentrations
Concentration (pM / mL)
18000
12000
6000
0
0 minutes
60 minutes
120 minutes
Time
Subject 1
Subject 2

FIG. 1

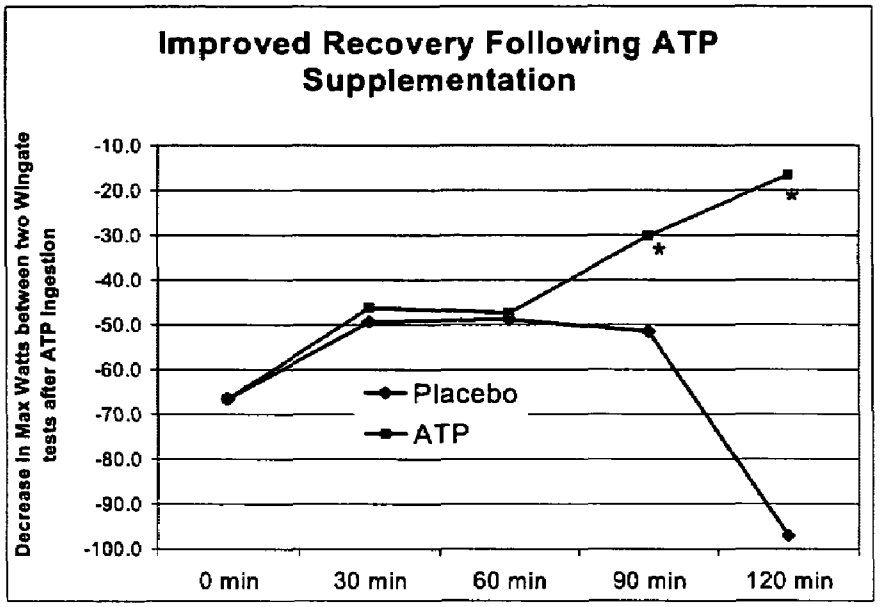

Improved Recovery Following ATP Supplementation
Decrease in Max Watts between two Wingate tests after ATP Ingestion
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-80.0
-90.0
-100.0
0 min
30 min
60 min
90 min
120 min
Placebo
ATP
*
*

FIG. 2

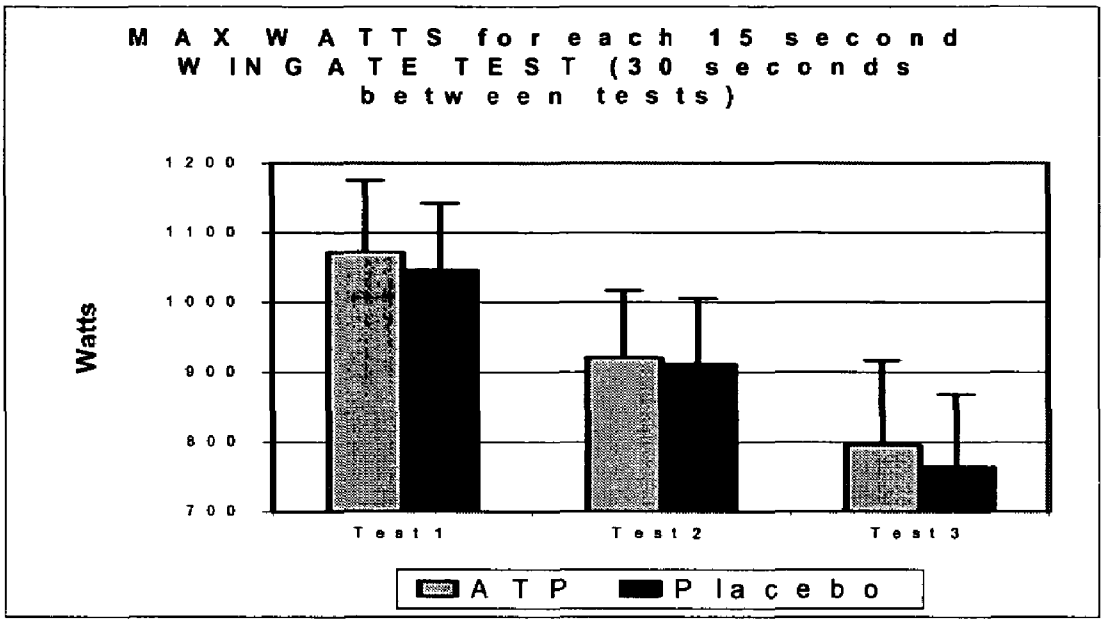

MAX WATTS for each 15 second WINGATE TEST (30 seconds between tests)
Watts
1200
1100
1000
900
800
700
Test 1
Test 2
Test 3
ATP
Placebo

FIG. 3

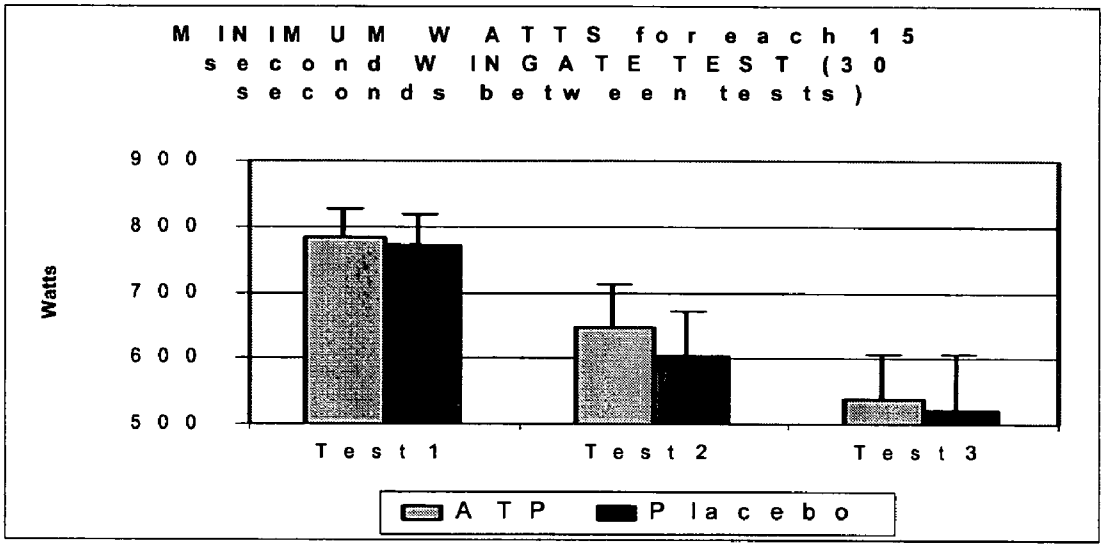

MINIMUM WATTS for each 15 second WINGATE TEST (30 seconds between tests)
Watts
900
800
700
600
500
Test 1
Test 2
Test 3
ATP
Placebo

FIG. 4

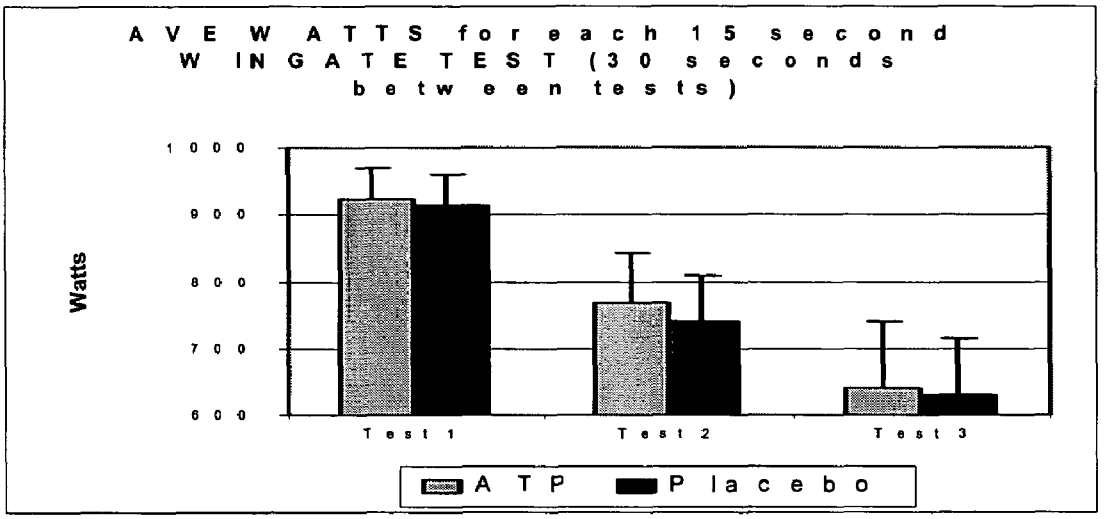

AVE WATTS for each 15 second WINGATE TEST (30 seconds between tests)
Watts
1000
900
800
700
600
Test 1
Test 2
Test 3
ATP
Placebo

FIG. 5

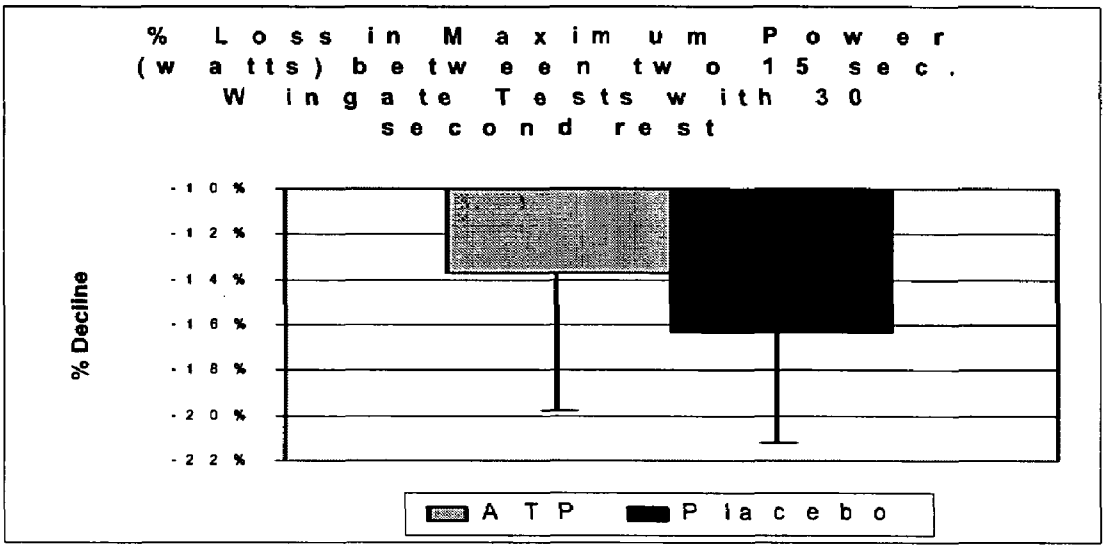

% Loss in Maximum Power (watts) between two 15 sec. Wingate Tests with 30 second rest
% Decline
-10%
-12%
-14%
-16%
-18%
-20%
-22%
ATP
Placebo

FIG. 6

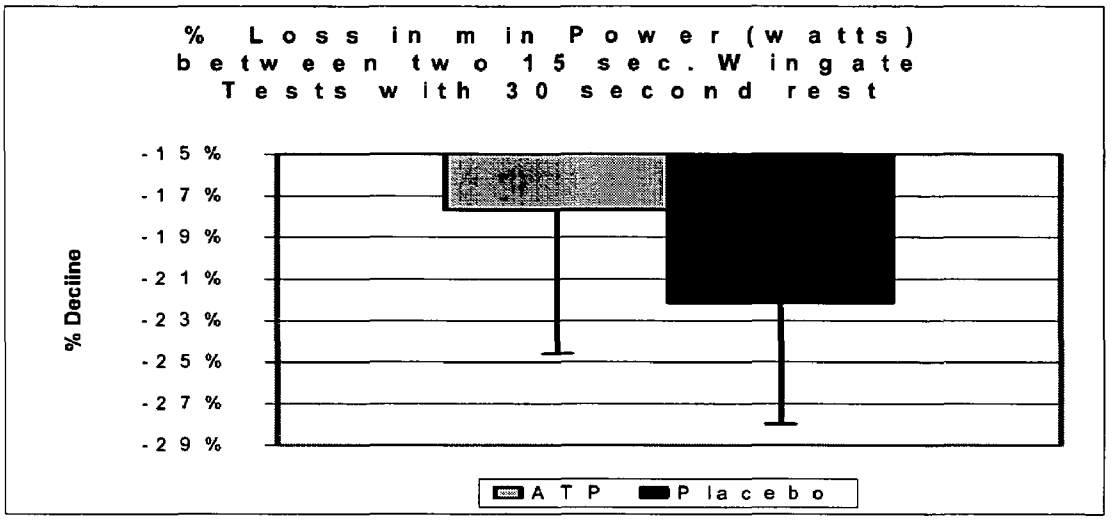

% Loss in min Power (watts) between two 15 sec. Wingate Tests with 30 second rest
% Decline
-15 %
-17 %
-19 %
-21 %
-23 %
-25 %
-27 %
-29 %
ATP
Placebo

FIG. 7

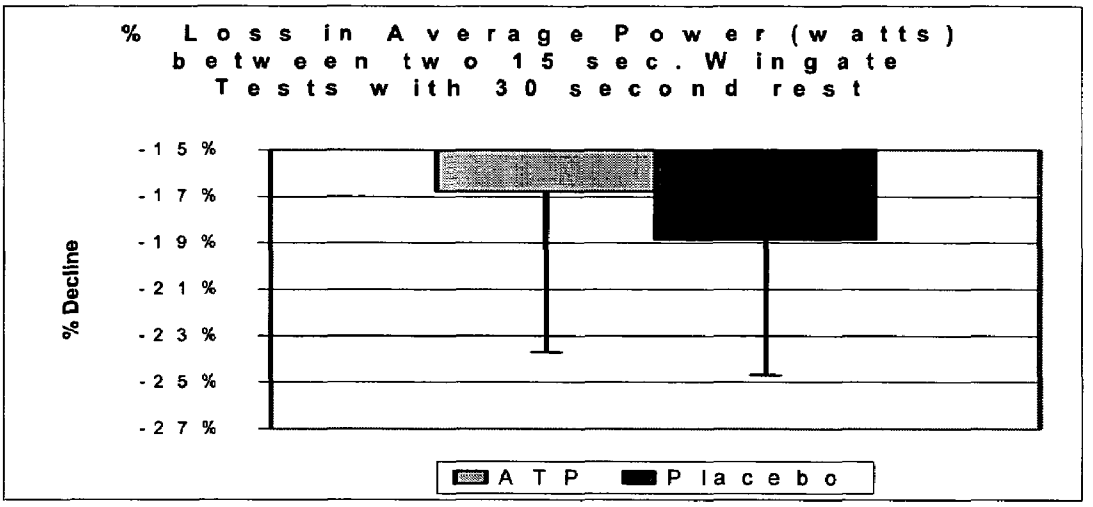

% Loss in Average Power (watts) between two 15 sec. Wingate Tests with 30 second rest
% Decline
-15 %
-17 %
-19 %
-21 %
-23 %
-25 %
-27 %
ATP
Placebo

FIG. 8

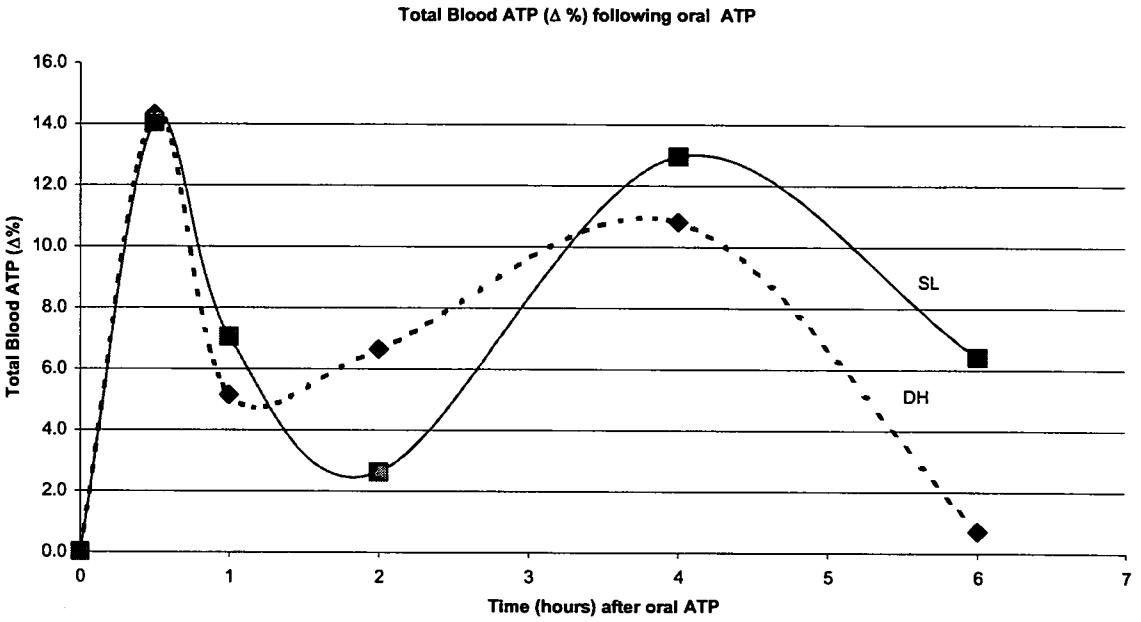

Total Blood ATP (Δ %) following oral ATP
Total Blood ATP (Δ%)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
1
2
3
4
5
6
7
Time (hours) after oral ATP
SL
DH

FIG. 9

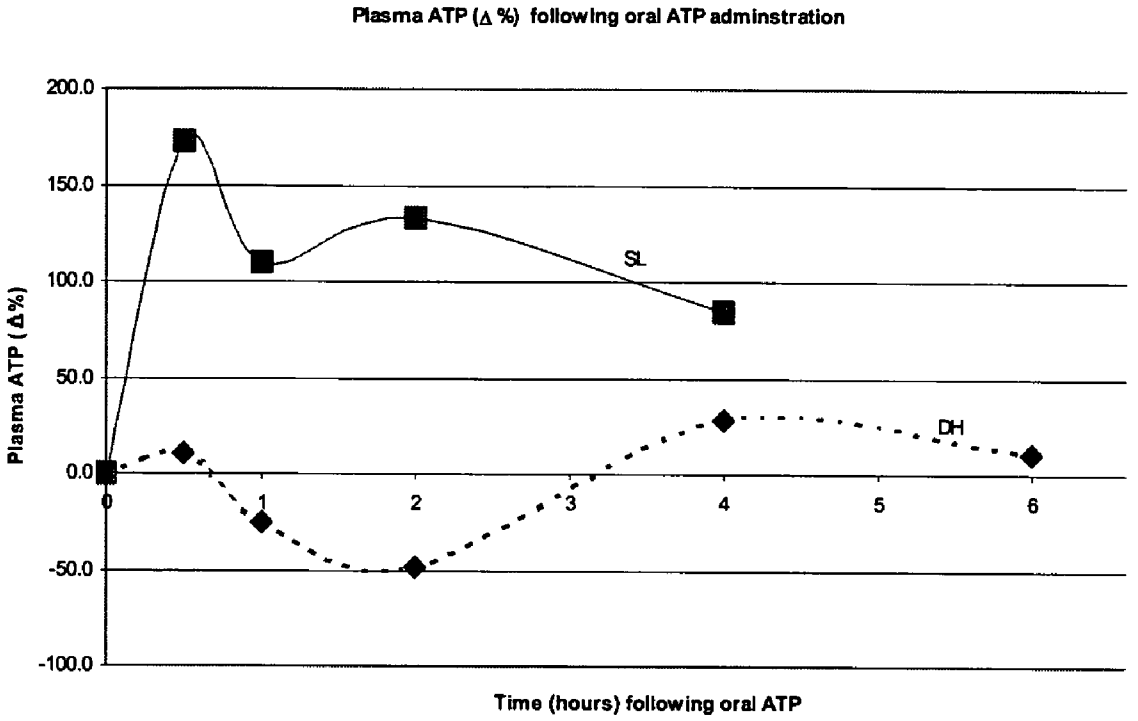

Plasma ATP (Δ %) following oral ATP adminstration
200.0
150.0
100.0
50.0
0.0
-50.0
-100.0
Plasma ATP (Δ%)
SL
DH
0
1
2
3
4
5
6
Time (hours) following oral ATP

FIG. 10

TABLE 1. Data represent total plasma ATP (μM) and blood ATP (mmols/Hct) parameters for 27 subjects receiving high dose ATP (225 mg), low dose ATP (150 mg), or placebo treatment.

			Plasma (ATP μM) and Blood (ATP mmols/Hct)					
			Acute Dosing (Pre-Ingestion)		Acute Dosing (Post-Ingestion)		Post	
Group	N	Hct (%)	Plasma	Blood	Plasma	Blood	Plasma	Blood
High	9	42.03 (2.0)	0.21 (0.1)	1.79 (0.3)	0.19 (0.1)	1.98 (0.1)	0.26 (0.1)	1.76 (0.3)
Low	9	41.63 (2.1)	0.20 (0.1)	1.77 (0.2)	0.23 (0.1)	1.94 (0.3)	0.26 (0.4)	1.72 (0.2)
Placebo	9	42.24 (2.8)	0.19 (0.1)	1.74 (0.2)	0.21 (0.2)	1.80 (0.5)	0.22 (0.1)	1.63 (0.1)

Hct (%), percentage of hemocrit.
Variables expressed as mean (SE).
Post refers to that testing period following 14 days of supplementation.

FIG. 11

TABLE 2. Data represent Wingate performance and blood lactic acid concentration for 27 subjects receiving high dose ATP (225 mg), low dose ATP (150 mg), or placebo treatment.
Variables expressed as mean (SE).
Post refers to that testing period following 14 days of supplementation.

		Wingate Test 1			Wingate Test 2		
	Group	Baseline	Acute Dosing	Post	Baseline	Acute Dosing	Post
Total Work (KJ)	High	23.39 (3.0)	23.72 (2.0)	22.92 (2.0)	22.42 (3.0)	20.99 (2.0)	19.86 (3.0)
	Low	24.45 (2.5)	23.44 (2.0)	24.27 (2.5)	22.18 (3.0)	20.99 (4.0)	21.36 (3.0)
	Placebo	25.12 (3.0)	24.46 (3.0)	24.45 (2.0)	22.76 (4.0)	21.76 (4.0)	21.79 (3.0)
Average PO (Watts)	High	779.70 (36.9)	790.55 (26.7)	763.96 (26.0)	747.43 (34.7)	699.77 (24.9)	661.93 (27.6)
	Low	814.85 (29.8)	781.22 (31.6)	808.95 (35.8)	739.32 (34.6)	712.64 (27.3)	712.06 (26.9)
	Placebo	837.38 (35.8)	815.50 (29.1)	814.94 (26.5)	758.60 (48.5)	725.48 (46.7)	726.44 (37.4)
Peak PO (Watts)	High	1550.22 (102.5)	1569.89 (51.5)	1417.00 (56.7)	1495.11 (57.7)	1415.22 (60.3)	1434.44 (59.7)
	Low	1511.11 (55.5)	1462.67 (42.3)	1473.56 (21.8)	1421.78 (25.5)	1407.67 (45.1)	1428.44 (23.3)
	Placebo	1577.11 (57.8)	1543.44 (30.6)	1481.78 (26.8)	1488.56 (56.1)	1487.67 (77.1)	1430.78 (24.9)
Post Wingate Lactate (mmol/L)	High	7.86 (0.7)	7.72 (0.5)	8.47 (0.5)	10.09 (0.8)	9.90 (0.5)	11.03 (0.6)
	Low	9.07 (0.4)	9.16 (0.7)	9.49 (0.9)	11.61 (0.6)	10.78 (0.7)	11.27 (0.9)
	Placebo	17.57 (9.4)	8.26 (0.7)	8.93 (0.8)	10.61 (0.6)	10.26 (0.4)	10.91 (0.8)

FIG. 12

TABLE 3. Data represent 1-RM bench press and strength indices for 27 subjects receiving high dose ATP (225 mg), low dose ATP (150 mg), or placebo treatment.

	Group	Baseline	Acute Dosing	Post
1-RM (kg)	High	123.03 (20.9)	131.16 *(24.6)	129.60(25.9)
	Low	114.80 (9.1)	119.35 (35.0)	119.35 (35.0)
	Placebo	118.99 (22.7)	120.91 (19.1)	116.92 (18.2)
70% 1-RM (kg)	High	86.06 (15.5)	93.59 (17.3)	91.51 (18.2)
	Low	80.91 (24.5)	83.54 (24.5)	83.54 (24.5)
	Placebo	83.94 (15.0)	85.20 (13.6)	82.07 (13.2)
Set 1 repetitions	High	13.77(4.0)	14.89 (4.0)	16.32† (3.0)
	Low	13.55 (4.0)	13.44 (4.0)	13.86 (5.0)
	Placebo	14.94 (4.0)	15.00 (4.0)	15.88 (3.0)
Set 2 repetitions	High	9.44 (3.0)	7.99 (2.0)	8.12 (1.0)
	Low	6.99 (2.0)	7.26 (3.0)	7.22 (3.0)
	Placebo	6.67 (3.0)	6.23 (3.0)	6.87 (2.0)
Set 3 repetitions	High	6.34 (3.0)	5.99 (2.0)	6.12 (2.0)
	Low	4.77 (2.0)	4.22 (2.0)	4.66 (2.0)
	Placebo	4.44 (2.0)	4.43 (2.0)	4.99 (2.0)
Total Lifting	High	2497.02 (220.9)	2350.76 (278.0)	3201.06 † (184.3)
Volume (kg)	Low	2025.40 (242.1)	2131.11 (309.6)	2544.24 (357.7)
	Placebo	2174.09 (216.5)	2182.32 (250.4)	2603.54 (218.1)

*P < 0.05 vs. baseline, †P < 0.01 vs. baseline.

Variables expressed as mean (SE).
Post refers to that testing period following 14 days of supplementation.

FIG. 13

Table 4. Data represent individual and group mean change data for 1-RM bench press testing. Each value is compared to baseline and presented in kg.

Subject	Group	Acute	Post
Sub 1	High	6.8	6.8
Sub 2	High	21.4	21.4
Sub 3	High	6.8	6.8
Sub 4	High	0.0	0.0
Sub 5	High	0.0	0.0
Sub 6	High	0.0	0.0
Sub 7	High	28.6	28.6
Sub 8	High	0.0	0.0
Sub 9	High	7.3	7.3
	Mean	7.9	7.9
	SEM	3.5	3.5
Sub 10	Low	0.0	0.0
Sub 11	Low	0.0	0.0
Sub 12	Low	7.3	0.0
Sub 13	Low	7.3	0.0
Sub 14	Low	6.8	0.0
Sub 15	Low	21.4	0.0
Sub 16	Low	0.0	0.0
Sub 17	Low	0.0	0.0
Sub 18	Low	0.0	0.0
	Mean	4.7	0.0
	SEM	2.4	0.0
Sub 19	Placebo	0.0	0.0
Sub 20	Placebo	0.0	-7.3
Sub 21	Placebo	6.8	0.0
Sub 22	Placebo	7.3	0.0
Sub 23	Placebo	0.0	0.0
Sub 24	Placebo	6.8	0.0
Sub 25	Placebo	-7.3	-21.4
Sub 26	Placebo	0.0	0.0
Sub 27	Placebo	14.5	-7.3
	Mean	3.2	-1.6
	SEM	2.1	1.1

FIG. 14

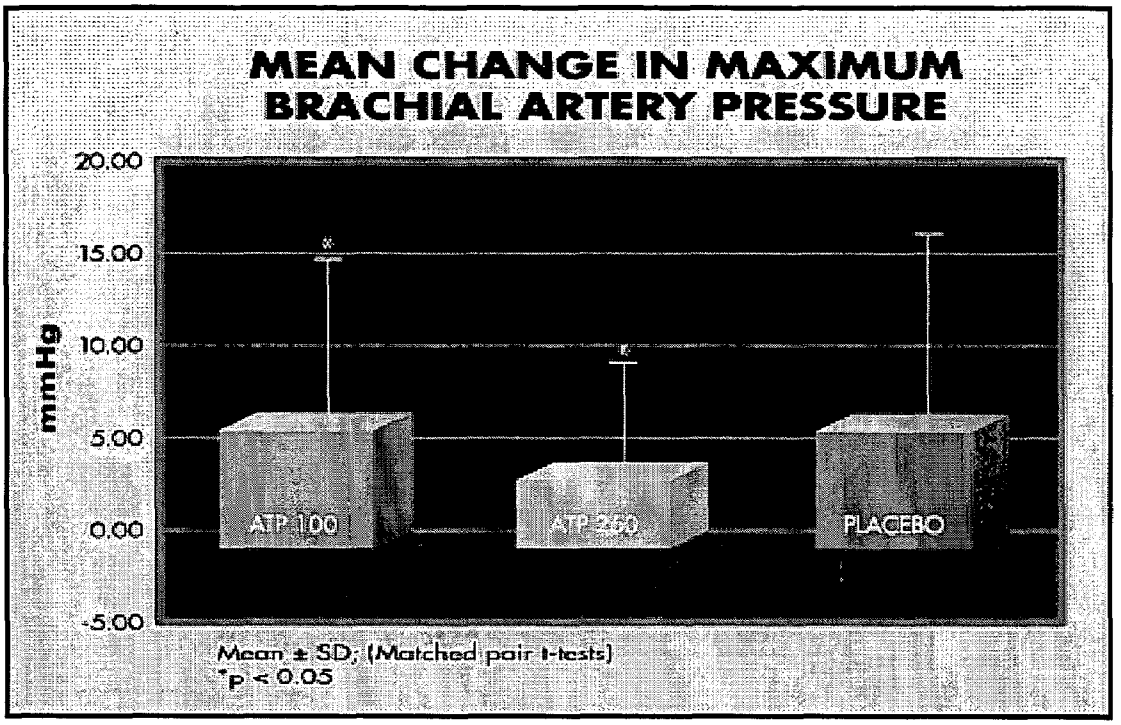

MEAN CHANGE IN MAXIMUM BRACHIAL ARTERY PRESSURE
20.00
15.00
10.00
5.00
0.00
-5.00
mmHg
ATP 100
ATP 250
PLACEBO
Mean ± SD; (Matched pair t-tests)
*P < 0.05

FIG. 15

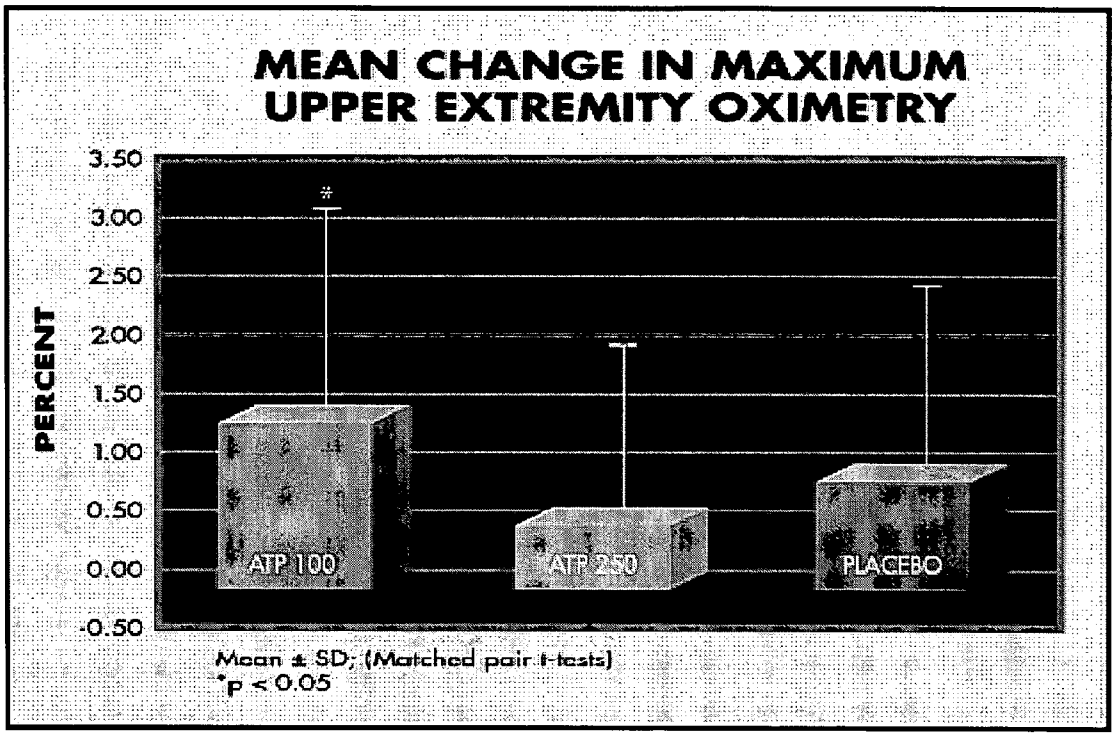

MEAN CHANGE IN MAXIMUM UPPER EXTREMITY OXIMETRY
PERCENT
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
#
ATP 100
ATP 250
PLACEBO
Mean ± SD; (Matched pair t-tests)
*p < 0.05

FIG. 16

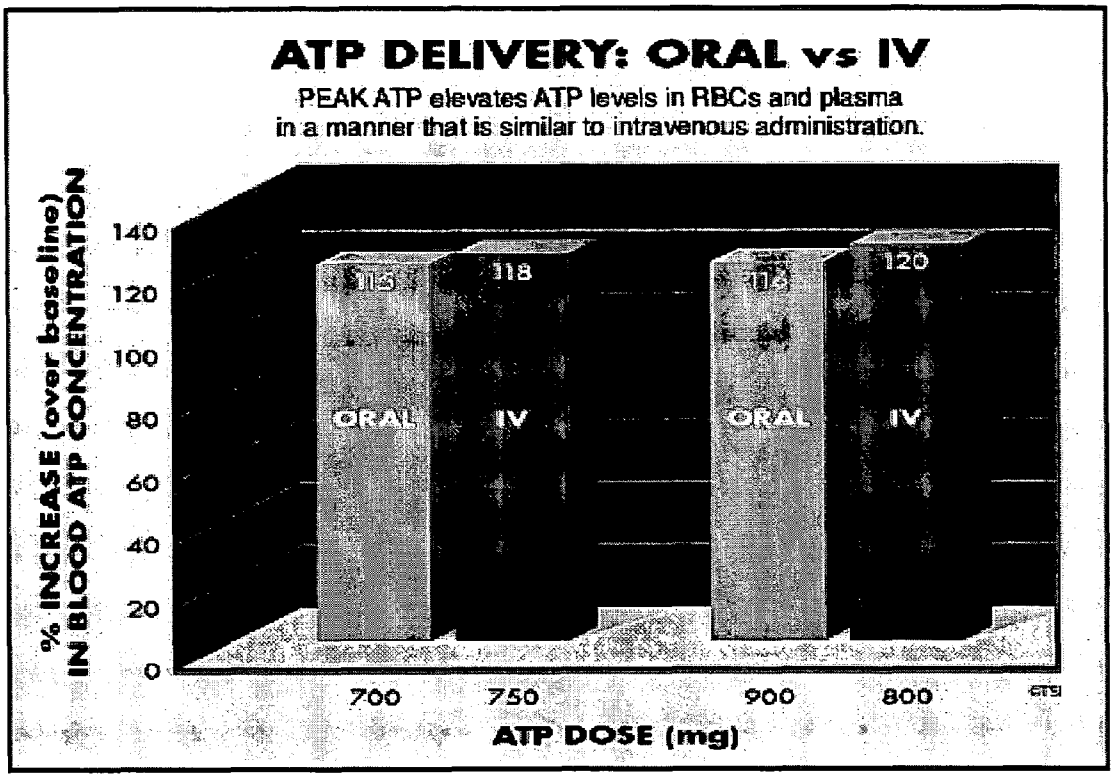

ATP DELIVERY: ORAL vs IV
PEAK ATP elevates ATP levels in RBCs and plasma
in a manner that is similar to intravenous administration.
% INCREASE (over baseline)
IN BLOOD ATP CONCENTRATION
140
120
100
80
60
40
20
0
118
120
ORAL
IV
ORAL
IV
700
750
900
800
ATP DOSE (mg)

FIG. 17

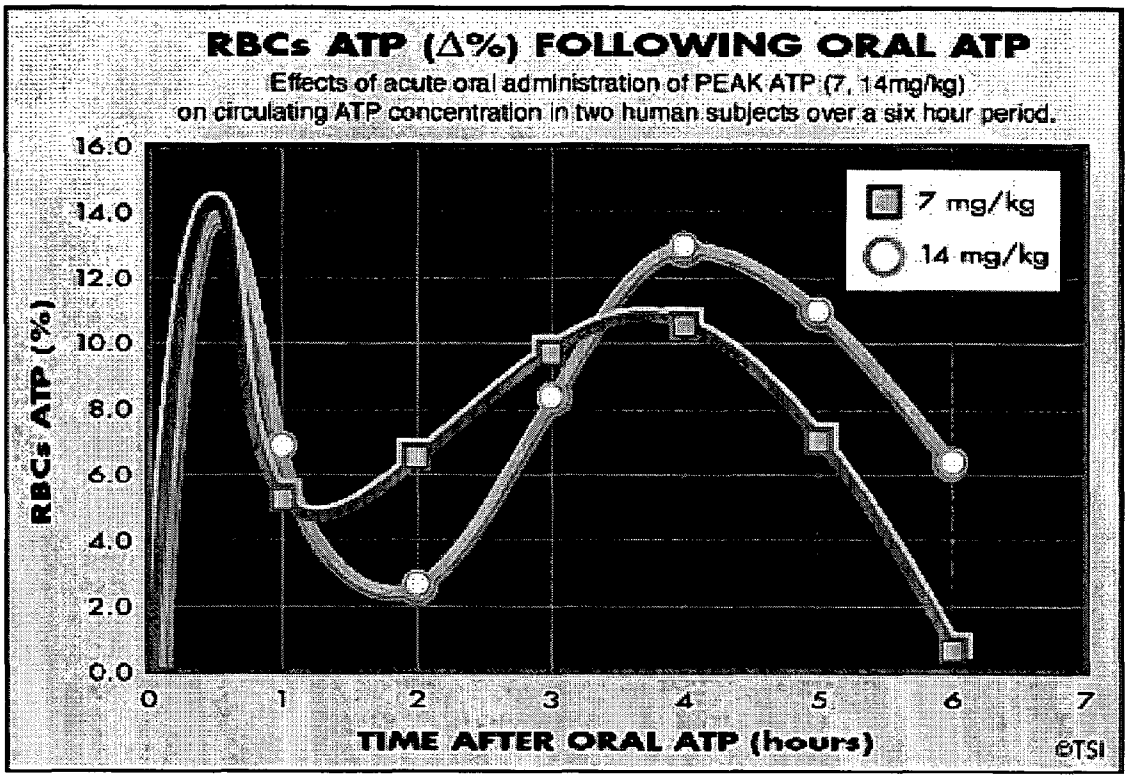

RBCs ATP (Δ%) FOLLOWING ORAL ATP
Effects of acute oral administration of PEAK ATP (7, 14mg/kg)
on circulating ATP concentration in two human subjects over a six hour period.
RBCs ATP (%)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
1
2
3
4
5
6
7
TIME AFTER ORAL ATP (hours)
7 mg/kg
14 mg/kg
©TSI

FIG. 18

METHOD FOR INCREASING MUSCLE MASS AND STRENGTH THROUGH ADMINISTRATION OF ADENOSINE TRIPHOSPHATE

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/549,181, filed Mar. 2, 2004, and entitled "METHOD FOR INCREASING MUSCLE MASS AND STRENGTH THROUGH ADMINISTRATION OF ADENOSINE TRIPHOSPHATE," and is a continuation-in-part of U.S. patent application Ser. No. 10/162,143, filed Jun. 3,2002, now abandoned and entitled "METHOD FOR INCREASING HUMAN PERFORMANCE BY REDUCING MUSCLE FATIGUE AND RECOVERY TIME THROUGH ORAL ADMINISTRATION OF ADENOSINE TRIPHOSPHATE," which claims priority to U.S. Provisional Patent Application Ser. No. 60/295,705, filed Jun. 4, 2001, and entitled "METHOD FOR INCREASING HUMAN PERFORMANCE BY REDUCING MUSCLE FATIGUE AND RECOVERY TIME THROUGH ORAL ADMINISTRATION OF ADENOSINE TRIPHOSPHATE," all of which are incorporated herein by reference.

BACKGROUND

1. Field of the Invention

This invention relates to the use of adenosine triphosphate (ATP) and, more particularly, to novel systems and methods for administration of ATP for the enhancement of muscle mass and/or strength.

2. The Background

The biological importance of adenosine triphosphate (ATP) first became apparent with the discovery of ATP in muscle tissue infusions by Fiske and Lohmann et al. in 1929. A. Szent-Gyorgi took the next logical step by demonstrating that ATP played an important role in muscle contraction. His experiments involved the addition of ATP to muscle fibers and then observing the subsequent contractions. Various researchers and those skilled in the art have progressively elucidated the role of ATP in muscle function since then. From these beginnings came the understanding and appreciation that ATP is the essential energy production molecule for every cell in the body. Similar phosphate-rich compounds are also found in every organism with ATP related compounds supplying all cellular energy. In 1982, Chaudry at the Yale Medical School published results showing that ATP was present in intracellular and interstitial fluids, thereby suggesting ATP's greatly expanded biological importance.

ATP and its breakdown product adenosine are also inherently involved in a number of extracellular processes like that of muscle contraction as described above. For example, some of the extracellular processes involving ATP may include neurotransmission, cardiac function (e.g., cardiac output, stroke volume, heart rate), platelet function, vasodilatation, perfusion (e.g., arterial pressure, cardiac output, total peripheral resistance), and liver glycogen metabolism.

As can be appreciated, these additional biological roles have given rise to various clinical applications of ATP and adenosine. For example, clinical applications may include applications of ATP and adenosine as aneuropathic and ischemic anaesthesia, ahypotensive agent for trauma or disease induced hypertension such as pulmonary hypertension, a mild hypoglycemic in type II diabetes, and at least preliminary evidence that ATP may be useful as an adjunctive therapy for radiation cancer treatment.

ATP and related compounds have been researched extensively for possible drug uses (see, Daly, J. Med. Chem., 25:197, (1982)). The most widespread of these clinical applications is in various cardiac treatments including the prevention of reperfusion injury after cardiac ischemia or stroke, the treatment of hypertension (see, Jacobson, et al., J. Med. Chem., 35, 407-422 (1992)), as well as the treatment of paroxysmal supra ventricular tachycardia (see, Pantely, et al., Circulation, 82, 1854 (1990)).

With regards to human performance specifically, the splitting of ATP to form adenosine diphosphate (ADP) is of critical importance in the functioning of muscle, since this is the reaction that directly supplies energy to myosin and actin to facilitate normal muscular contraction. In many cases, this requirement is met by the actual rebuilding of ATP as it is used, rather than by storing a very large amount of ATP in the muscle. However, under exceptionally demanding conditions, such as peak athletic performance or certain deficiency states induced by either inadequate nutrition or various diseases, ATP availability could prove to be a limiting step in actuating peak muscle output.

While therapeutic uses of ATP in various disease states is quite common, applications of ATP relating to possible benefits such as increased athletic performance in normal, healthy individuals appear to be largely absent in the published literature.

A method of increasing intracellular ATP through orally administered precursors of adenosine triphosphate in dietary supplements for treatment of reduced energy availability resulting from strenuous physical activity, illness, or trauma appears to be disclosed in U.S. Pat. No. 6,159,942. However, ATP itself is not administered; rather pentose sugars are administered individually, mixed into dry food or in solution. Specifically, the preferred pentose is D-ribose, singly or combined with creatine, pyruvate, L-carnitine, and/or vasodilating agents.

As appreciated by those skilled in the art, the mechanism of action for ribose to stimulate ATP production is through the phosphorylation of nucleotide precursors that may be present in the tissues. These are converted to adenosine monophosphate (AMP) and further phosphorylated to ATP. Adenosine is directly phosphorylated to AMP, while xanthine and inosine are first ribosylated by 5-phosphoribosyl-1-pyrophosphate (PRPP) and then converted to AMP. In the de novo synthetic pathway, ribose is phosphorylated to PRPP, and condensed with adenine to form the intermediate AMP. AMP is further phosphorylated via high energy bonds to form adenosine diphosphate (ADP) and ATP.

In certain circumstances, ATP can cross directly into the cell without the need for intracellular de novo synthesis. Chaudry (1982) explained that exogenous ATP crosses cellular membranes when depletion occurs within myosin units. ATP or ATP substrates may access human physiology orally, sublingually, or intravenously. Carbohydrates, oral ATP, or oral-sublingual ATP may be consumed for enhancing endurance performance and for preventing muscle exertion or heat stress cramps. Therefore, methods of delivering actual ATP to the bloodstream and subsequently to interstitial fluids may have benefits not associated with mere ATP precursors.

In addition to exhibiting the proper therapeutic effect, any method for delivering actual ATP to muscle cells in an attempt to prevent depletion must also include a consideration of the realities of the practical administration of a therapeutic agent in a daily athletic environment. First, the therapeutic agent must be suitable for sale as a dietary supplement, and/or functional food and not only as a drug. This requires that the therapeutic agent have certain technical and economic char-

acteristics related to the dietary supplement and/or functional food industries. From a technical standpoint, the therapeutic agent should preferably be orally administered and suitable for inclusion in a variety of dosage forms such as tablets or capsules or may be included in-solid foods mixed into dry food or in solution. Additionally, the therapeutic agent should also be well tolerated vis a vis digestion and suitably stable both ex vivo and in vivo. From an economic standpoint, a therapeutic agent should ideally be robust enough for combination with a variety of other ingredients without the need for special handling during manufacture or special processing, packaging, or storing of the resulting composition or mixture.

ATP is generally known to be subject to degradation from exposure to high temperature and/or high humidity conditions and in the presence of a low pH, such as that found in stomach acid. It is therefore desirable to protect administered ATP from degradation by stomach acid through the use of a low. pH insoluble compound, such as a protective enteric coating. Sublingual ATP preparations, which are not generally subject to exposure to gastric fluids, exist but they are not typically suitable for inclusion in a variety of dosage forms and complex formulations. This creates the need to coat supplements containing currently available ATP (such as adenosine-5'-triphosphate disodium) to impart protective enteric properties after the final dosage form is manufactured.

While the technique of enteric coating has been applied to finished ATP dosage forms such as capsules and tablets, it has not been applied to bulk ATP preparations suitable for inclusion in alternate dosage forms common to nutritional supplements and/or functional food products such as liquids, nutrition bars, and powders, as well as, the above-mentioned tablets and capsules.

Consistent with the foregoing, an ideal ATP preparation should include protective enteric properties independent of the final dosage form, thus eliminating the need for potential customers to impart enteric protection during manufacture since this capability is both expensive and uncommon. And, additionally providing enteric protection for finished food dosage forms such as liquids, bars, and powders is not presently possible.

SUMMARY AND OBJECTS OF THE INVENTION

In view of the foregoing, it is a primary object of the present invention to provide novel systems and methods for increasing muscle mass and/or strength through administration of adenosine triphosphate (ATP).

In addition, it is an object of the present invention to provide novel systems and methods for delivering and/or administration of ATP in a manner that protects the ATP from degradation by gastric juices through enteric coating to enhance absorption into the blood stream and provide additional therapeutic benefit when compared with non-protected forms of ATP.

It is also an object of the present invention to provide novel systems and methods for coating ATP for enteric administration that are compatible with manufacture of foods, drugs, and dietary supplements of complex formulation and various dosage forms including capsules, tablets, caplets, lozenges, liquids, sublingual, solid foods, powders, and other conceivable dosage forms, as applicable, without the need for imparting enteric properties to the entire mixture, any other part of the mixture, or finished products.

It is a further object of the present invention to provide novel systems and methods for increasing muscle mass and/or strength through delivery and/or administration of ATP using any pharmaceutical delivery form, for example and not by way of limitation, tablet, capsule, powder, granule, microgranule, pellet, soft-gel, controlled-release form, liquid, solution, elixir, syrup, suspension, emulsion, magma, gel, cream, ointment, lotion, transdermal, sublingual, ophthalmic form, nasal form, otic form, aerosol, inhalation form, spray, parenteral form (e.g., intravenous, intramuscular, subcutaneous), suppository, and the like.

It is a still further object of the present invention to provide novel systems and methods for increasing muscle mass and/or strength through delivery and/or administration of ATP using any nutraceutical delivery form, for example and not by way of limitation, tablet, capsule, powder, granule, microgranule, pellet, soft-gel, controlled-release form, liquid, solution, elixir, syrup, suspension, emulsion, magma, gel, cream, ointment, lotion, transdermal, sublingual, ophthalmic form, nasal form, otic form, aerosol, inhalation form, spray, parenteral form (e.g., intravenous, intramuscular, subcutaneous), suppository, and the like.

In addition, it is an object of the present invention to provide novel systems and methods for increasing muscle mass and/or strength through delivery and/or administration of ATP using any functional food delivery form, for example and not by way of limitation, bar, beverage, bread, cereal, cracker, egg, juice and juice drink, milk and soft cheese, mineral water, pasta, pasta sauce, probiotic drink soya product, spread, stimulation/energy beverage, yogurt, baby and/or children's food, women's product, men's product, meal replacement, and the like.

Also, it is an object of the present invention to provide novel systems and methods for increasing muscle mass and/or strength through delivery and/or administration of ATP which may be used in combination with other amino acids, botanicals, functional foods, herbals, nucleotides, nutraceuticals, nutrients, pharmaceuticals, proteins, vitamins, and/or the like.

It is a further object of the present invention to provide novel systems and methods for increasing organ perfusion and/or organ function through delivery and/or administration of an effective amount of ATP, alone or in combination with other amino acids, botanicals, functional foods, herbals, nucleotides, nutraceuticals, nutrients, pharmaceuticals, proteins, vitamins, and/or the like.

It is a still further object of the present invention to provide novel systems and methods for reducing pain perception by inhibiting sensory nerves and/or nociceptors through administration of an effective amount of ATP, alone or in combination with other amino acids, botanicals, functional foods, herbals, nucleotides, nutraceuticals, nutrients, pharmaceuticals, proteins, vitamins, and/or the like.

Also, it is an object of the present invention to provide novel systems and methods for increasing cognitive function and/or promoting a sense of well-being through delivery and/or administration of an effective amount of ATP, alone or in combination with other amino acids, botanicals, functional foods, herbals, nucleotides, nutraceuticals, nutrients, pharmaceuticals, proteins, vitamins, and/or the like.

Consistent with the foregoing objects, the present invention provides systems and methods for delivering and/or administering an effective amount of ATP for increasing muscle mass and/or muscle strength. Said systems and methods may deliver and/or administer ATP in a manner that protects the ATP from degradation by gastricjuices through enteric coating to enhance absorption into the blood stream and provide additional therapeutic benefit when compared with non-protected forms of ATP. In addition, said systems and methods may deliver and/or administer an effective

amount of ATP for enhancing organ perfusion, enhancing organ function, reducing the pain perception (i. e., anti-nociceptor function), and/or promoting an enhanced sense of well-being. In preferred embodiments of the present invention, a gastric acid secretion inhibitory coating may be applied to the effective amount of ATP in a manner that protects the ATP from degradation by gastric juices. As contemplated herein, the effective amount of ATP may be delivered by means of any conventional pharmaceutical, nutraceutical, or functional food delivery form.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects and features of the present invention will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only typical embodiments of the invention and are, therefore, not to be considered limiting of its scope, the invention will be described with additional specificity and detail through use of the accompanying drawings in which:

FIG. **1** is a graph illustrating the changes in ATP blood plasma concentrations over 120 minutes following administration of one presently preferred embodiment of an ATP composition of the present invention;

FIG. **2** is a graph illustrating improvements in muscle recovery following. supplementation with one presently preferred embodiment of an ATP composition of the present invention;

FIG. **3** is a graph illustrating the difference max watts between placebo and one presently preferred embodiment of an ATP composition of the present invention for three (3) successive ergonometic tests;

FIG. **4** is a graph illustrating the difference in minimum watts between placebo and one presently preferred embodiment of an ATP composition of the present invention for three (3) successive Wingate tests;

FIG. **5** is a graph illustrating the average watts between placebo and one presently preferred embodiment of an ATP composition of the present invention for three (3) successive Wingate tests;

FIG. **6** is a graph illustrating the percentage loss in maximum power between placebo and one presently preferred embodiment of an ATP composition of the present invention during a thirty (30) second Wingate test;

FIG. **7** is a graph illustrating the percentage loss in maximum power between placebo and one presently preferred embodiment of an ATP composition of the present invention during a fifteen (15) second Wingate test;

FIG. **8** is a graph illustrating the percentage loss in average power between placebo and one presently preferred embodiment of an ATP composition of the present invention during a thirty (30) second Wingate test;

FIG. **9** is a graph illustrating an example of one presently preferred embodiment of a percentage change in total blood ATP in two human subjects over six (6) hours;

FIG. **10** is a graph illustrating an example of one presently preferred embodiment of a percentage change in plasma ATP in two human subjects over six (6) hours;

FIG. **11** is a table illustrating an example of one presently preferred embodiment of total plasma and blood ATP parameters for twenty-seven (27) study participants receiving high dose ATP (i.e., 225 mg), low dose ATP (i.e, 150 mg), or placebo treatment;

FIG. **12** is a table illustrating an example of one presently preferred embodiment of the results of the Wingate performance tests blood lactic acid concentration;

FIG. **13** is a table summarizing an example of one presently preferred embodiment of the results of the 1-RM bench press and strength indices for twenty-seven (27) study participants receiving high dose ATP (i. e., 225 mg), low dose ATP (i. e, 150 mg), or placebo treatment;

FIG. **14** is a table illustrating an example of one presently preferred embodiment of the change in individual and group mean data for 1-RM bench press testing;

FIG. **15** is a graph is provided which illustrates the results of an example of one presently preferred embodiment of mean change in maximum brachial artery pressure following administration of one presently preferred embodiment of an ATP composition of the present invention;

FIG. **16** is a graph which illustrates the results of an example of one presently preferred embodiment of mean change in maximum upper extremity oximetry following administration of one presently preferred embodiment of an ATP composition of the present invention in human subjects;

FIG. **17** is a graph that illustrates that presently preferred embodiments of the ATP compositions of the present invention administered in an oral formulation achieve increases in blood ATP concentration (i. e., RBC ATP concentrations) that are consistent with increases achieved by intravenous formulations of ATP; and

FIG. **18** shows a graph that illustrates one presently preferred embodiment of the effects on RBC ATP concentration following oral administration of a presently preferred embodiment of the ATP compositions of the present invention in human subjects.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It will be readily understood that the components of the present invention, as generally described and illustrated in the Figures herein, could be modified, arranged and designed in a wide variety of different configurations. Thus, the following more detailed description of the embodiments of the systems and methods of the present invention, as represented in the Examples and FIGS. **1** through **18**, is not intended to limit the scope of the invention. The scope of the invention is as broad as claimed herein.

Oral administration of ATP is usually in the form of Adenosine-5'-Triphosphate Disodium. For the purpose of contemplating the breadth and scope of the present invention, Adenosine-5'-Triphosphate Disodium or any form of ATP or adenosine suitable for oral administration may be combined with any of the known coatings suitable for imparting enteric properties in granular form.

Granular formation or agglomeration may be achieved by means of any conventional method including for example, but not by way of limitation, fluidized bed granulation, wet granulation, or spherical rotation agglomeration. Subsequent enteric coatings may include, for example and not by way of limitation, methacrylic acid-acrylic acid copolymers, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and acetate succinate, shellac, polyethylene glycol, polysorbates, carboxymethylcellulose or polyoxyethylene-polyoxypropylene glycol. Furthermore, the objects of the present invention may be at least partially accomplished through the use of quasi-enteric coatings or materials such as those which result in delayed or timed release of active ingredients such as sugars, castor oil, microcrystalline cellulose, starches such as maltodextrin or cyclodextrin, or food-grade gums or resins.

A water barrier overcoat may then be applied to assist in isolating the ATP active from other formulation ingredients, as well as to provide protection versus environmental degradation.

In human performance enhancing formulations, the resulting ATP may be incorporated into the delivery and/or administration form in a fashion so as to result in a typical dosage range of about twenty-five (25) mg to about two-hundred and twenty-five (225) mg, though more or less may be desirable depending on the application and other ingredients. In one presently preferred embodiment of the present invention, an effective dosage range may be administered in divided dosages, such as two (2) to three (3) times per day for maximum effectiveness.

For the purposes of establishing definitional support for various terms that are used in the present application, the following technical comments and review are provided:

"Ergogenic" may be defined as the ability to increase capacity for bodily and/or mental labor, especially by reducing or eliminating signs and symptoms of fatigue. "Anaerobic" may be literally defined as without oxygen. "Anaerobic exercise" may be defined as exercise which does not increase the body's requirement for oxygen. Typically, anaerobic exercise may be a short-burst, higher-intensity exercise. Proteins and carbohydrates may be utilized to build muscle mass and/or strength. Fat burning may be an indirect effect of anaerobic exercise. Anaerobic exercise may include, for example and not by way of limitation, push-ups, pull-ups, sit-ups, sprinting, stomach crunches, weight lifting, strength training, and the like.

"Aerobic" may be literally defined as with oxygen. "Aerobic exercise" may be defined as exercise which increases the body's requirement for oxygen. Typically, aerobic exercise involves an increased respiratory (i.e., breathing) rate and cardiac (i.e., heart) rate over an extended period of time. Following approximately twenty (20) minutes of aerobic exercise, the body usually requires the utilization of stored fat deposits as fuel for muscle contraction. Therefore, aerobic exercise may be considered to have a direct fat burning effect. Aerobic exercise may include, for example and not by way of limitation, basketball, bicycling, cross-country skiing, ice hockey, ice skating, jogging, martial arts, rollerblading, rowing, soccer, swimming, tennis, walking (e.g., fast), and the like.

"Bench press" may be defined as a muscular strength test and a method for conducting strength training. Typically, bench press exercises involve at least one repetition of extending weight in a perpendicular direction from the chest while the body is in a supine position.

"Wingate test" may be defined as a cycle ergometer test used to measure muscle work over a relatively short period (e.g., thirty (30) seconds), and may also be used to measure a fatigue index.

"Perfusion" may be defined as the pumping of a fluid through an organ or tissue. Typically, perfusion may be used to describe the volume and/or effectiveness of supplying blood to any one or more of the organs in the body of a human or animal. Perfusion may be used to enhance the function of an organ, for example and not by way of limitation, the brain, liver, heart, lung, kidney, nerve, muscle, intestine, and the like.

The following examples will illustrate the invention in further detail. It will be readily understood that the composition of the present invention, as generally described and illustrated in the Examples herein, could be synthesized in a variety of formulations and dosage forms. Thus, the following more detailed description of the presently preferred embodiments of the methods, formulations, and compositions of the present invention, as represented in Examples I-VIII is not intended to limit the scope of the invention, as claimed, but it is merely representative of the presently preferred embodiments of the invention.

EXAMPLE I

In one presently preferred embodiment of an ATP composition of the present invention, twenty-one (21) mg of Adenosine-5'-Triphosphate Disodium was entabletted in a Stokes B2, sixteen (16) station tablet press using ⅜" standard concave punch dies. The resulting tablets included microcrystalline cellulose as an inert filler and less than three percent (3%) magnesium stearate as a lubricant. Total tablet weight was about 350 mg and the resulting tablet hardness was approximately 12 kp. The tablet cores were then coated with ten percent (10%) methacrylate copolymer (Eudragit from Rohm, Germany).

The resulting tablets comprising one presently preferred embodiment of the ATP composition of the present invention were then given to two (2) healthy male volunteers, ages fifty-one (51) and fifty-seven (57), respectively, for the purpose of evaluating the ability of the present invention to deliver ATP to blood plasma. Referring now to FIG. **1**, a graph shows the increase in ATP blood plasma concentration levels from zero (0) to 120 minutes following oral administration of one presently preferred ATP composition of the present invention in the two (2) human subjects.

As these results clearly illustrate, the ATP composition of the present invention results in dramatically increased ATP blood plasma concentrations in a manner consistent with effective enteric delivery.

EXAMPLE II

In one presently preferred embodiment of an ATP composition of the present invention, twenty-five (25) mg of Adenosine-5'-Triphosphate Disodium was entabletted in a Stokes B2, sixteen (16) station tablet press using ⅜" standard concave punch dies. The resulting tablets included microcrystalline cellulose as an inert filler and less than three percent (3%) magnesium stearate as a lubricant. Total tablet weight was about 350 mg and the resulting tablet hardness was approximately 12 kp. The tablet cores were then coated with ten percent (10%) methacrylate copolymer (Eudragit from Rohm, Germany).

The resulting tablets comprising one presently preferred embodiment of the ATP composition of the present invention were then given to twenty-one (21) volunteers for the purpose of evaluating the effectiveness of the ATP composition of the present invention as an aid to enhancing human performance. The study demographics may be summarized as follows:

		Avg Weight (kg)	Age (years)	Number in Group (n)
Control:	Males	84.5	26.1	6
	Females	63.1	30.7	4
ATP:	Males	76.1	28.0	7
	Females	58.0	22.4	4

Doses were given in double blind fashion, wherein neither the recipient nor the researcher was aware of active versus placebo administration. Results were measured using a standard Wingate test for measuring endurance.

As appreciated by those skilled in the art, since the 1970's, the Wingate test has become "one of the most widely recognized protocols in exercise research for determining peak muscle power and indirectly reflecting anaerobic capacity." (See, Roberg and Roberg, Exercise Physiology, Musky Publishers 1997) The test consists of pedaling or arm cranking at maximal effort for 30 seconds against a constant load. The Wingate test may be used to quantify the mean and peak power that are generated during the test. The decline in power that may occur during the Wingate test may be defined as a fatigue index.

The application of the test in the present example specifically sought to measure muscle recovery following the administration of a single Wingate maximal effort test lasting fifteen seconds by contrasting the output with a second Wingate maximal effort test conducted immediately following the first test. The results were measured for a period of 120 minutes with the first pair of tests conducted beginning two hours after administration of the ATP composition of the present invention and then again every thirty minutes thereafter.

Referring now to FIG. **2**, the results of the experiment are illustrated in graph form. In particular, the vertical axis may show the decrease in Max Watts between the first and second Wingate tests after ingestion of the ATP composition of the present invention. The horizontal axis may show the change in time between zero (0) and 120 minutes. As shown in FIG. **2**, notable differences in muscle recovery may be observed at 90 minutes and 120 minutes following the administration of the ATP composition. These results show significant improved muscle recovery and substantially less depletion of maximal output versus placebo following administration of the ATP composition of the present invention. Moreover, the results of the study also indicate a persistent effect that peaks sometime around or after 120 minutes.

EXAMPLE III

Using the same tablet preparation of one presently preferred embodiment of an ATP composition of the present invention as used in Example II, another series of tests were conducted to evaluate the effects of a single dose (containing about twenty-five (25) mg ATP) of the present invention on various parameters measuring performance using three back-to-back Wingate tests. The first test was administered two hours after oral administration of the tablet prepared in accordance with one presently preferred method of producing an ATP composition of the present invention. Referring generally to FIGS. **3-8**, the results of Example III may be illustrated as several different measurements of a series of anaerobic and other exercises tests.

Referring specifically to FIG. **3**, a bar graph illustrates one presently preferred embodiment of a level of maximum muscle output during the entire 15 second test for each of the three back-to-back tests following administration of the ATP composition of the present invention versus placebo.

As shown in FIG. **4**, a bar graph illustrates one presently preferred embodiment of a level of minimum muscle output during the entire 15 second test for each of the three (3) back-to-back tests following administration of the ATP composition of the present invention versus placebo.

Referring now to FIG. **5**, a bar graph shows one presently preferred embodiment of a level of average muscle output during the entire 15 second test for each of the three (3) back-to-back tests following administration of the ATP composition of the present invention versus placebo.

Referring now to FIG. **6**, a bar graph illustrates one presently preferred embodiment of a decrease in maximum muscle output between the first (1st) and second (2nd) Wingate test following administration of the ATP composition of the present invention versus placebo.

As shown in FIG. **7**, a bar graph shows one presently preferred embodiment of a decrease in minimum muscle output between the first (1 st) and second (2nd) Wingate test following administration of the ATP composition of the present invention versus placebo.

Referring now to FIG. **8**, a bar graph illustrates one presently preferred embodiment of a decrease in average muscle output between the first (1st) and second (2nd) Wingate test following administration of the ATP composition of the present invention versus placebo.

EXAMPLE IV

In yet another presently preferred embodiment of a method for preparing an ATP composition of the present invention, Adenosine-5'-Triphosphate Disodium may be agglomerated into granules using a seed crystal nucleus upon which a mixture containing ATP and various excipients for binding and flow are progressively loaded using a fluidized bed processor. The base granulation formula of one presently preferred embodiment may include the following, for example and not by way of limitation:

20% ATP
20% Microcrystalline Cellulose
20% Starch
35% Sucrose
5% Maltodextrin

The resulting agglomeration prepared as outlined above may then be dried with a loss of weight on drying of about one percent (1%) to about four percent (4%), and yielding a granule from about 100 microns to about 1000 microns in size with an active ATP "drug" load of approximately ten percent (10%) to about thirty percent (30%). The loaded particles may then be coated with about fifteen percent (15%) to about forty percent (40%) aqueous enteric coating containing approximately sixty-three percent (63%) (Emcoat 120N)), aboutl 9.5% Hydroxypropylmethylcellulose (HPMC), about 12.5% Oleic acid and about 5% Triacetin. In one presently preferred embodiment, the prepared granules may be encapsulated in two (2)-piece hard gelatin capsules using microcrystalline cellulose as a filler and less than three percent (3%) magnesium stearate as a lubricant.

EXAMPLE V

Using the same tablet preparation of one presently preferred embodiment of the ATP composition of the present invention consumed in Examples II and III, another test was conducted to evaluate the bioavailability (i.e., the degree and rate at which a substance may be absorbed into a living system or otherwise made available at a site of physiological activity) of a single dose (containing an average about 850 mg ATP) of the ATP composition of the present invention. The tablets containing the ATP composition of the present invention were given to two volunteers for the purpose of evaluating relative changes in intracellular and extracellular ATP levels following the dosage. The dosage was administered on an empty stomach, whereby the volunteers had fasted from midnight until the test, about eight (8) hours later. One volunteer received a dose of about 15 mg active ATP/kg and the second volunteer received a dose of about 7.5 mg active ATP/kg.

A baseline blood ATP level was obtained immediately prior to dosage administration and additional ATP blood levels were obtained at intervals of thirty (30) minutes, one (1) hour, two (2) hours, four (4) hours, and six (6) hours following dosage administration. Referring now to FIGS. **9** and **10**, the results of this test are illustrated.

Referring specifically to FIG. **9**, a graph is provided which illustrates the results of an example of one presently preferred embodiment of a percentage change of the concentration of ATP in total blood in two human subjects over six (6) hours following dosage administration. Referring now to FIG. **10**, a graph is provided which illustrates the results of an example of one presently preferred embodiment of a percentage change in concentration of ATP in plasma in two human subjects over six (6) hours following dosage administration.

The experiment outlined in the present Example specifically sought to measure the presence of a pharmacokinetic dose-response within the intracellular and extracellular body compartments following the administration of a single dosage of a presently preferred embodiment of the ATP composition of the present invention.

FIGS. **9** and **10** demonstrate that there is a measurable relationship between the oral administration of an effective amount of the ATP compositions of the present invention and alterations in blood and plasma concentrations of ATP in the body of the participants. Moreover, FIGS. **1** through **8** demonstrate a measurable relationship between the oral administration of an effective amount of the ATP compositions of the present invention and human physical performance testing. These data show that the compositions of the present invention provide a method for effecting intracellular and extracellular ATP concentrations and increasing human performance by reducing muscle fatigue and recovery time which comprises administering an effective amount of ATP to a human in need of such treatment.

EXAMPLE VI

Increasing Anaerobic Capacity

There has been significant interest in the conception and development of ergogenic substances over at least the past twenty years. For example, creatine monohydrate has enjoyed much popularity as an aid to short duration, high-intensity exercise performance, sometimes referred to as anaerobic exercise.

In search of additional ergogenic substances, those skilled in the art may appreciated that ATP may play an important role in muscle function. However, the full range of ATP effects on the muscle and body have remained unknown. For example, ATP is known to be involved in neurotransmission, cardiac function, and in platelet function (e.g., blood clotting). Difficulties in effective delivery of ATP during exercise, however, may have hindered and/or prevented previous investigation of ATP effects.

In the midst of anaerobic exercise, the muscles and other organs of the body may depend upon ATP, glycogen, and phosphocreatine to supply the energy to continue biochemical reactions. As appreciated, ATP, glycogen, and phosphocreatine may not be stored in significant amounts by the body. Therefore novel systems and methods for effectively supplementing the body's stores of ATP may be helpful in meeting demands of anaerobic exercise. A study was conducted to evaluate the effect of one presently preferred embodiment of an ATP composition of the present invention on anaerobic exercise performance values, which is outlined as follows:

Study Inclusion Criteria:

Thirty healthy males were recruited to participate in a trial at The Cooper Institute (Dallas, Tex.) for a series of three high-intensity anaerobic power assessments. Participation inclusion criteria included: (1) male gender; (2) age between eighteen and forty-five years; (3) at least a six month creatine free interval prior to the study; and (4) current involvement in a strength training program (i.e., two to four times a week for at least twelve months). Participants were asked to refrain from any vigorous physical activity for twenty-four hours prior to assessment and asked to fast for at least 3 hours prior to assessment. Twenty-seven participants completed the study.

Study Design:

Anaerobic exercise performance were evaluated on three separate occasions via the completion of two Wingate tests. The occasions for evaluation preferably occurred at a baseline evaluation period, an acute evaluation period (i.e., seven days following baseline, one hour following initial ATP composition or placebo administration), and after fourteen days of supplementation with ATP composition or placebo. Wingate tests were performed on a Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands). During each testing period, all subjects reported to the testing lab at the same time of day for each successive measurement.

Each subject was allowed to warm up for a period of approximately fifteen minutes on the testing ergometer. More specifically, the warm-up period may include ten minutes of general steady state pedaling, followed by five minutes of intermittent short sprinting pedaling. Each Wingate test began with a thirty second period of unload pedaling. Each subject was instructed to begin pedaling at a slow, self-selected pace. A subject was provided with a verbal countdown at the ten second mark to give the subject sufficient time to achieve maximum pedal cadence by the beginning of the test.

Following the countdown period, tension may be automatically added to the ergometer and each subject may pedal as fast as possible for thirty seconds against a flywheel resistance set at 0.08 mg per kg of body mass. Verbal encouragement to the subject may be continued throughout the test. Each subject may complete two. Wingate tests separated by five minutes of rest. The same flywheel resistance may be used for each Wingate test.

Each subject was also be evaluated for blood lactate accumulation at three minutes following each Wingate test. A whole blood sample was evaluated for lactic acid using an Analox GM7 Micro-Stat Lactate Analyzer™ (London, UK). Whole blood lactic acid was obtained from each subject using a finger stick (i.e., puncture) procedure and collection in capillary tubes which contained heparin, fluoride, and nitrite. Fluoride may be used as a glycolysis inhibitor and nitrite may be used to convert hemoglobin to the methemoglobin form to prevent uptake or egress of oxygen from the sample. The analysis of the blood sample was performed within two to three minutes of sample collection.

In addition, before each of the acute and post testing assessment periods, a 2.5 mL blood sample was collected through venipuncture and transferred to a vacutainer containing ethylenediaminetetracetic acid potassium salt (EDTA K_3) solution (Vacutainer, Becton Dickinson Company, Franklin Lakes, N.J.). Shear stress to the sample was minimized by releasing the vacuum prior to sample collection.

Immediately following sample collection, 1 mL of blood was transferred from the EDTA K_3 solution tube into a 1.5 mL Eppendorf tube with 0.2 mL of polymer separtor gel and centrifuged for two to three minutes at 6000×g at 4° C. A

firefly luciferase assay was performed by a 12-detector luminometer (Perkin-Elmer Bioscienc, Boston, Mass.) on the blood sample to determine ATP concentrations which may be down to the subnanomolar concentration range.

As appreciated by those skilled in the art, numerous sample collection and analysis techniques may be available to evaluate the blood lactate accumulation. Accordingly, the collection and analysis techniques set forth in the present Example are merely exemplary of one present preferred embodiment of the present invention and is not intended to limiting of the breadth and scope of the methodologies of the present invention.

Primary outcome variables from the Wingate tests included peak anaerobic power, which may be characterized as: (i) the greatest output (i.e., peak output—"PO") in power (i.e., "W") achieved during the test; (ii) the total amount of work exhibited during the entire thirty second testing period; and (iii) the average PO produced during the thirty second testing period. The total work produced for each ten second period of the test (i.e., 0-10 seconds, 11-20 seconds, and 21-30 seconds, respectively) were also observed and evaluated.

Each subject participant was examined on three separate occasions, as follows: (I) baseline; (ii) acutely (i.e., seven days after baseline and seventy-five minutes following ATP administration); and (iii) after fourteen days of ATP administration (i.e., twenty-one days following baseline).

Following baseline testing, each subject was assigned, in a randomized, double-blind fashion, to receive either a high dose (i.e., 225 mg) of enterically coated ATP, a low dose (i.e., 150 mg) of enterically coated ATP, or a visibly similar placebo. Seven days following the baseline test, each subject returned to the lab to undergo an acute dose evaluation phase. Supplementation with ATP or placebo began seventy-five minutes prior to the acute test and continued for fourteen days of supplementation.

As appreciated in the art, ATP may be coated to improve delivery, administration and/or bioavailability. Coated ATP may have protection against decomposition by acid in the gastrointestinal system. In addition, coated ATP may lead to improved absorption of ATP into the systemic circulation.

Results:

Referring now to FIG. **11**, the results of the blood ATP concentrations are illustrated in table form. As noted from reviewing the results set forth in the table, there was no statistically significant difference in the blood sample measured parameters. While animal trials have previously shown significant results in the absorption of purine nucleotides (e.g., ATP) and accumulation in the bloodstream, that significant change was not apparent in this study. However, transient increases in ATP concentration may be suggestive that there is some transport beyond the portal system. The relatively larger size for the ATP molecule may be at least partly responsible for this observation. It is possible that other delivery systems, alone or in combination with enteric-coated systems, may provide a greater ATP blood concentration.

Referring now to FIG. **12**, the results of the Wingate tests and blood lactic acid concentration are illustrated in table form. As noted from reviewing the results set forth in the table, there were no significant changes between the baseline, acute, and post-treatment phases of the evaluation period.

EXAMPLE VII

Increasing Muscular Mass and/or Strength

Another aspect of anaerobic performance may be muscle mass and/or muscular strength. Strength conditioning training and research has been the subject of significant interest in the conception and development of ergogenic substances. As with other tests of anaerobic capacity, creatine monohydrate has become popular as an aid to building muscle mass and/or strength.

It has been found that the use of ATP during a muscle strength and condition program results in greater stores of ATP and thus greater capacity for building muscle strength. Therefore, novel systems and methods for effectively supplementing the body's stores of ATP may be helpful in meeting demands of anaerobic exercise. A study was conducted to evaluate the effect of one presently preferred embodiment of an ATP composition of the present invention on anaerobic exercise performance values, which is outlined as follows:.

Study Inclusion Criteria:

Thirty healthy males were recruited to participate in a trial study at The Cooper Institute (Dallas, Tex.) for a series of three high-intensity anaerobic power assessments. Participation inclusion criteria included: (1) male gender; (2) age between eighteen and forty-five years; (3) at least a six month creatine free interval prior to the study; and (4) current involvement in a strength training program (i.e., two to four times a week for at least twelve months). Participants were asked to refrain from any vigorous physical activity for twenty-four hours prior to assessment and asked to fast for at least three hours prior to assessment. Twenty-seven participants completed the study.

Study Design:

Increase in muscle mass and/or strength were evaluated on three separate occasions via the completion of a 1-repetition maximum (RM) bench press test, and three sets of repetitions to fatigue at seventy percent (70%) of 1RM. The occasions for evaluation occurred at a baseline evaluation period, an acute evaluation period (i.e., seven days following baseline and one hour following initial ATP composition or placebo administration), and after fourteen days of supplementation with ATP composition or placebo. 1-RM bench press tests and repetitions to fatigue were performed on a Universal bench press machine with dynamic variable resistance. Test reliability of the 1RM test has been shown to be highly correlated over a period of nine days.

Five minutes after completing a 1RM test, each subject completed three sets of repetitions to fatigue, with two minutes between each set. For each subject and at each evaluation session (i.e., baseline, acute, post-fourteen days supplementation), the 1RM value (kg), the 70% 1RM value (kg), and the number of repetitions for each set were recorded. In addition a total lifting volume (TLV; in kg) may be calculated with the following equation:

$$TLV=[70\%\ 1RM \times \text{set 1 reps}]+[70\%\ 1RM \times \text{set 2 reps}]+[70\%\ 1RM \times \text{set 3 reps}]$$

During each testing period (i.e., evaluation session), all subject participants reported to the testing lab at the same time of day for each successive measurement.

Results:

Referring now to FIG. **13**, the results of the strength testing study outlined hereinabove are described in the table. There was one statistically significant difference and there were several within group statistical differences, especially in the group receiving high dose ATP. In the 1RM bench press test, those receiving the high dose ATP composition had a significant increase at the acute evaluation period compared to the baseline measurements. In addition, the TLV for those in the high dose group increased after fourteen days of supplemen-

tation compared to the baseline values. Moreover, the high dose ATP group experienced an increase in the set 1 repetitions to fatigue. The change in individual and group mean data for 1-RM bench press testing is set forth in the table illustrated in FIG. **14**.

In addition to the above-identified results, those in the high dose ATP group also reported an improved sense of well-being during their participation in the study. This effect may be due to the role of ATP as a neurotransmitter and/or pain perception modifying agent. Previous research may suggest the possibility of ATP and similar nucleotides in the alteration of central nervous system responses. In particular, these effects may be mediated through the noradrenaline, glutamine, and serotonin neurotransmitter systems. Moreover, pain modifying effects may be accomplished through the stimulation of Adenosine receptors (e.g., sub-type 1 and sub-type 2).

EXAMPLE VIII

Increases in Perfusion Pressure, Oximetry, and Erythrocyte ATP Concentration

Preferred embodiments of the present invention may be used at dosages of between about 7 mg ATP/kg body weight and about 14 mg ATP/kg body weight to evaluate the effects on perfusion pressure, oximetry, and erythrocyte ATP concentration in human subjects. As appreciated, ATP effectively increases the body's extracellular levels of ATP. The normal aging process in humans and animals and stress on the body are known to reduce extracellular ATP levels.

Following ingestion, preferred embodiments of the ATP compositions of the present invention may be broken down in the small intestine into free adenosine and free phosphate components. These components may be rapidly absorbed and subsequently absorbed into liver cells and red blood cells to expand ATP pools. Red blood cell (RBC) ATP pools may be slowly released into the blood plasma and this supplemental ATP activates specialized ATP receptors on the surface of vascular endothelial cells. The activation of endothelial cells may result in improved blood vessel tone and relaxation of the vessel walls so that more blood may be able to move through the vessels to the heart, lungs, brain, and peripheral vasculature, as well as other organs.

Referring now to FIG. **15**, a graph is provided which illustrates the results of an example of one presently preferred embodiment of mean change in maximum brachial artery pressure (i.e., in the upper extremity) following administration of one presently preferred embodiment of an ATP composition of the present invention. These increases in maximum brachial artery pressure did not adversely affect heart rate or blood pressure. Moreover, increases in organ perfusion may result in enhanced delivery of glucose, nutrients, and oxygen to peripheral sites. Increases in organ perfusion may also result in more efficient removal of catabolic waste products from organs and other tissues in the body.

As shown in FIG. **16**, a graph is provided which illustrates the results of an example of one presently preferred embodiment of mean change in maximum upper extremity oximetry (i. e., degree of oxygen saturation in the circulating blood) following administration of one presently preferred embodiment of an ATP composition of the present invention in human subjects. When oxygen saturation is low in the body, RBCs may act as sensors and signal for the release of additional ATP into the bloodstream. This may result in multiple physiological effects. For example, and not by limitation, regulation of vascular tone to reduce pulmonary and systemic vascular resistance without adversely affecting blood pressure or heart rate may stimulate blood flow. Enhanced perfusion to the heart, lungs, brain, and other tissues may promote a more active lifestyle, boost mental acuity, improve muscle mass and function, improve physical performance, lessen perception of exercise-induced pain, and may relieve cold hands and feet.

Referring now to FIG. **17**, a graph is provided that illustrates that presently preferred embodiments of the ATP compositions of the present invention administered in an oral formulation may achieve increases in blood ATP concentration (i.e., RBC ATP concentrations) that are consistent with increases achieved by intravenous formulations of ATP. In contrast, numerous prior art methods and compositions have taught that ATP may not be absorbed in sufficient quantities to achieve these concentrations. The present example, however, demonstrates sufficient intracellular ATP levels may be achieved.

As shown in FIG. **18**, a graph is provided that illustrates one presently preferred embodiment of the effects on RBC ATP concentration following oral administration of a presently preferred embodiment of the ATP compositions of the present invention at dosages of 7 mg/kg and 14 mg/kg in human subjects.

In summary, the Examples disclosed herein demonstrate that the ATP compositions of the present invention provide a method for effecting intracellular and extracellular ATP concentrations in mammals. Additionally, the present invention substantially increases human performance by increasing endurance and muscle output through reduction in muscle fatigue and decrease in muscle recovery time after exhaustion. Moreover, the present invention provides systems and methods for delivering oral administration of ATP in a manner that protects it from degradation by gastric juices through enteric coating to enhance absorption into the blood stream or through avoiding exposure to gastric juices by sublingual administration, and provide additional therapeutic benefit when compared with non-protected forms.

The Examples outlined herein further illustrate systems and methods for enterically coating ATP compatible with manufacture of foods, drugs, and dietary supplements of complex formulation and various dosage forms without the need for imparting enteric properties to the entire mixture, any other part of the mixture, or finished products.

In addition, the Examples disclosed herein illustrate systems and methods for using enterically coated ATP for increasing anaerobic capacity, increasing muscle mass and/or strength, increasing organ perfusion, and increasing erythrocyte ATP concentrations. These properties may translate into declining the aging process, and/or enhancing energy, vitality, longevity, and athletic performance. The results represented in FIGS. **1** through **18** are statistically accurate.

The present invention may be embodied in other specific forms without departing from its structures, methods, or other essential characteristics as broadly described herein and claimed hereinafter. The described embodiments are to be considered in all respects only as illustrative, and not restrictive. The scope of the invention is, therefore, indicated by the appended claims, rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed and desired to be secured by United States Letters Patent is:

1. A method of increasing muscle strength in a mammal comprising the steps of administering to said mammal an effective amount of Adenosine Triphosphate ("ATP") to

increase muscle strength of muscles of the mammal while said mammal is participating in a strength training program.

2. The method of claim **1**, wherein the method further increases muscle mass of the mammal.

3. The method of claim **1**, wherein the method further increases total lifting volume of muscles of the mammal participating in a strength training program.

4. The method of claim **1**, wherein the effective amount of ATP is between about 150 mg and about 850 mg.

5. The method of claim **1**, wherein the effective amount of ATP is between about 7.5 mg ATP/kg body weight and about 14 mg ATP/kg body weight of the mammal.

6. The method of claim **1**, wherein the step of administering is selected from the group consisting of oral, parenteral, sublingual, topical, transdermal, intramuscular, and inhalation.

7. The method of claim **6**, wherein the oral administration comprises a delivery form selected from the group consisting of tablet, capsule, powder, granule, microgranule, pellet, soft-gel, controlled-release form, liquid, solution, elixir, syrup, suspension, emulsion, and magma.

8. The method of claim **1**, further comprising the step of introducing the effective amount of ATP into a functional food form.

9. The method of claim **1**, wherein the effective amount of ATP is combined with one or more compounds selected from the group consisting of amino acids, proteins, carbohydrates, botanicals, and herbals.

10. The method of claim **1**, wherein the effective amount of ATP is combined with branched-chain amino acids.

11. A method of increasing muscle mass in a mammal comprising the steps of administering to said mammal an effective amount of Adenosine Triphosphate ("ATP") to a mammal to increase muscle mass of the muscles while said mammal is participating in a strength training program.

12. The method of claim **11**, wherein the method further increases total lifting volume of the muscles of the mammal.

13. The method of claim **11**, wherein the effective amount of ATP is between about 150 mg and about 850 mg.

14. The method of claim **11**, wherein the effective amount of ATP is between about 7.5 mg ATP/kg body weight and about 14 mg ATP/kg body weight of the mammal.

15. The method of claim **11**, wherein the step of administering is selected from the group consisting of oral, parenteral, sublingual, topical, transdermal, intramuscular, and inhalation.

16. The method of claim **11**, wherein the oral administration comprises a delivery form selected from the group consisting of tablet, capsule, powder, granule, microgranule, pellet, soft-gel, controlled-release form, liquid, solution, elixir, syrup, suspension, emulsion, and magma.

17. The method of claim **11**, wherein the effective amount of ATP is combined with one or more compounds selected from the group consisting of amino acids, proteins, carbohydrates, botanicals, and herbals.

18. The method of claim **11**, wherein the effective amount of ATP is combined with branched-chain amino acids.

19. The method of claim **11**, further comprising the step of introducing the effective amount of ATP into a functional food form.

20. The method of claim **1** further comprising administering an effective amount of Adenosine Triphosphate ("ATP") and at least one amino acid, other than ATP, to said mammal.

21. The method of claim **20**, wherein the at least one amino acid comprises a branched-chain amino acid.

22. The method of claim **20**, wherein the at least one amino acid comprises arginine.

23. The method of claim **20**, wherein the amount of ATP is between about 7.5 mg ATP/kg body weight and about 14 mg ATP/kg body weight of the mammal.

24. The method of claim **11** further comprising administering an effective amount of Adenosine Triphosphate ("ATP") and at least one amino acid, other than ATP, to said mammal.

25. The method of claim **11**, wherein the at least one amino acid comprises a branched-chain amino acid.

26. The method of claim **11**, wherein the at least one amino acid comprises arginine.

27. The method of claim **11**, wherein the amount of ATP is between about 7.5 mg ATP/kg body weight and about 14 mg ATP/kg body weight of the mammal.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,629,329 B2
APPLICATION NO. : 11/069746
DATED : December 8, 2009
INVENTOR(S) : Lee et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

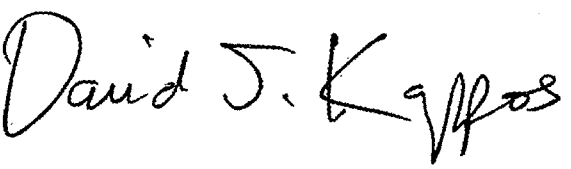
On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1082 days.

Signed and Sealed this

Second Day of November, 2010



David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT B

US007671038B1

(12) **United States Patent**
Rapaport

(10) **Patent No.: US 7,671,038 B1**
(45) **Date of Patent: Mar. 2, 2010**

(54) **METHOD OF THERAPEAUTIC TREATMENTS INCLUDING HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE AND OTHER CONDITIONS IN A HUMAN HOST BY ADMINISTERING ADENINE NUCLEOTIDES**

(76) Inventor: **Eliezer Rapaport**, 192 Payson Rd., Belmont, MA (US) 02178

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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A01N 43/04 (2006.01)
A61K 31/70 (2006.01)

(52) **U.S. Cl.** **514/46**; 514/47

(58) **Field of Classification Search** 514/45, 514/46

See application file for complete search history.

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(57) **ABSTRACT**

The administration of adenine nucleotides or adenosine and inorganic phosphate to a human host results in the generation of elevated liver, other organs and red blood cell adenosine 5'-triphosphate (ATP) pools as well as increased levels of ATP and adenosine in the extracellular blood plasma compartment of the blood. The present invention deals with the utilization of the elevated intracellular ATP levels and the elevated extracellular levels of ATP and adenosine for the treatment of a broad spectrum of clinical targets in HIV disease/AIDS and the achievement of decisive therapeutic gains.

22 Claims, No Drawings

METHOD OF THERAPEAUTIC TREATMENTS INCLUDING HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE AND OTHER CONDITIONS IN A HUMAN HOST BY ADMINISTERING ADENINE NUCLEOTIDES

TECHNICAL FIELD

The present invention is concerned with treating Human Immunodeficiency Virus infection, and/or Human Immunodeficiency Virus disease, and/or Acquired Immunodeficiency Syndrome related complex, and/or Acquired Immunodeficiency Syndrome, and/or Acquired Immunodeficiency Syndrome with secondary infections, by administering to a human host adenine nucleotides and/or adenosine and inorganic phosphate separately or in combination.

BACKGROUND ART

Acquired immunodeficiency syndrome (AIDS) is a disease resulting from human immunodeficiency virus (HIV) infection. The progression from the initial HIV infection to AIDS-related complex (ARC), AIDS, and AIDS with secondary-infections, which is the end stage of the disease, is long, variable in time and not completely understood (Weiss, R. A., How does HIV cause AIDS? Science 260:1273-1279 [1993]). Another recent review of HIV infection, the course that follows and the pathogenic mechanisms responsible for the clinical outcome is useful for up to date background purposes (Pantaleo, G., Graziosi, C. and Fauci, A. S. The immunopathogenesis of human immunodeficiency virus infection. New England Journal of Medicine 328:327-335 [19993]). A recently published broadly-encompassing article lists all the currently approved anti-HIV agents as well as drugs for the treatment of AIDS and its associated illnesses and secondary infections (Johnson, M. I. and Hoth, D. F., Present status and future prospects for HIV therapies. Science 260:1286-1293 [1993]). This article contains a broad outline of "Current State-of-the-Art Treatment", "Therapies in Development" and "The Future of HIV Therapeutics." An accompanying article of interest dealing with HIV therapeutic (rather than prophylactic) vaccine development is Haynes, B. F. Scientific and social issues of human immunodeficiency virus vaccine development. Science 260:1279-1286 [1993].

All the therapies which were developed or suggested for this disease up to now possess a narrow target, namely, they address a single aspect of the disease. The acknowledged therapies for HIV disease/AIDS are antiretroviral agents such as those approved (AZT or zidovudine, ddI or didanosine and DDC or zalcitabine) along with other antiretroviral agents which are now in clinical trials. The antiretroviral agents are divided into the following categories: reverse transcriptase inhibitors, protease inhibitors, Tat inhibitors, drugs that block viral entry into cells, and nucleic acid-based therapies. The other therapies currently in development are aimed at improving the immune system ("Immune Reconstitution") thus enabling the human host to control HIV infection and its progression. Another general approach to the treatment of AIDS is the development of therapeutic HIV vaccines whereby HIV-infected individuals are treated with viral immunogens designed to boost the anti-HIV immune response and eradicate viral particles along with decreasing the number of virus-infected cells.

U.S. Pat. No. 4,880,918 entitled "Arrest and Killing of Tumor Cells by Adenosine 5'-Diphosphate and Adenosine 5'-Triphosphate" to Rapaport, U.S. Pat. No. 5,049,372 entitled "Anticancer Activities in a Host by Increasing Blood and Plasma Adenosine 5'-Triphosphate (ATP) Levels" to Rapaport, and U.S. Pat. No. 5,227,371 entitled "Utilization of Adenine Nucleotides and/or Adenosine and Inorganic Phosphate for Elevation of Liver, Blood and Blood Plasma Adenosine 5'-Triphosphate Concentrations" to Rapaport, disclose the treatment of cancer by administration of adenine nucleotides to a human host and/or disclose a method to expand organ, blood and blood plasma ATP pools by administration of adenine nucleotides and/or adenosine and inorganic phosphate to a human host.

The role of intracellular ATP as a cellular energy source, a phosphate group donor for phosphorylation reactions and an allosteric regulator of the activities of a variety of cellular proteins has been well-established. Only in the past 10 years have the roles of adenosine and ATP began to emerge as powerful physiological extracellular modulators of intravascular, extravascular and CNS functions, a role which is attracting significant attention within the field of drug development (Williams, M. Purinergic drugs: opportunities in the 1990's. Drug Development Research 28:438-444 [1993]). Adenosine is the endogenous ligand for the A (or P_1) type purine receptors affecting mostly cardiovascular and CNS functions, whereas ATP is the ligand for P_2 type purine receptors and is now an accepted neurotransmitter (Benham, C. D. ATP joins the fast lane. Nature 359:103-104 [1992]; Edwards, F. A., Gibb, A. J. and Colquhoun, D. ATP receptor-mediated synaptic currents in the central nervous system. Nature 359:144-147 [1992]).

The administration of adenine nucleotides (e.g., ATP, AMP or other adenine nucleotides) into the systemic circulation results in the immediate degradation of the nucleotide to adenosine and inorganic phosphate. This degradation in the vascular bed is followed by incorporation of the adenosine and inorganic phosphate into liver ATP pools (steady state levels) yielding significant expansion of the liver ATP pools, which is followed by an expansion of red blood cell ATP pools. The red blood cells with expanded ATP pools which are produced by this mechanism slowly release micromolar levels of ATP into the blood plasma without undergoing hemolysis, thus achieving elevated steady state extracellular ATP levels, in spite of the catabolic enzymatic activities present intravascularly (Rapaport, E. and Fontaine, J. Anticancer activities of adenine nucleotides in mice are mediated through expansion of erythrocyte ATP pools. Proc. Natl. Acad. Sci. USA 86:1662-1666 [1989]). These elevated levels of ATP inhibit both tumor growth and host weight loss in tumor-bearing murine models. The inhibition of tumor growth proceeds by the receptor-mediated and non-receptor-mediated effects of extracellular ATP on the tumor cell membrane, whereas the inhibition of host weight loss in tumor-bearing hosts is the result of ATP-mediated marked slowdown of hepatic gluconeogenesis and reversal of the depletion of visceral energy stores (Rapaport, E. Mechanisms of anticancer activities of adenine nucleotides in tumor-bearing hosts. Ann. N.Y. Acad. Sci. 603:142-150 [1990]).

Administration of ATP by intravenous infusions at a dose of 50 μg/kg min for at least 48 hours yielded a doubling of blood (red blood cell) ATP levels after 24 hours in advanced cancer patients (most of whom were at stage III B or IV non-small cell lung cancer). Hyperuricemia developed only after at least 48 hours of continuous infusions (Haskell, C. M. and Sanchez-Anaya, D. Hyperuricemia as a complication of ATP: preliminary observation of a phase I clinical trial. ASCO Proceedings 12:435A [1993]) and could be easily dealt with by allopurinol. The elevated blood ATP levels declined within several days after termination of the ATP

infusions with a return of total blood ATP levels to their basal levels. In advanced cancer patients with cachexia and malnutrition, the basal blood ATP levels were lower than normal but could be elevated to well above a normal level after ATP infusions.

The mechanisms of expansion of organ ATP levels after administration of ATP proceed by both the increased supply of the major purine precursor for salvage ATP synthesis in cells (adenosine) and the interaction of extracellular ATP with membrane P_2-purine receptors which signals an enhanced intracellular ATP synthesis. Most of the expansions of total blood (red blood cell) ATP pools occur due to increased supply of purines to the mature erythrocyte in the hepatic sinusoids, where these purine precursors (mostly adenosine) arise from the increases in turnover of hepatic ATP pools (Rapaport, E. and Fontaine, J. Generation of extracellular ATP in blood and its mediated inhibition of host weight loss in tumor-bearing mice. Biochem. Pharmacol. 38:4261-4266 [1989]). A significant increase in red blood cell ATP pools of the magnitude observed in vivo after ATP administration cannot be obtained in vitro (Rapaport, E. and Fontaine, J. Anticancer activities of adenine nucleotides in mice are mediated through expansion of erythrocyte ATP pools. Proc. Natl. Acad. Sci. USA 86:1662-1666 [1989]).

Adenosine 5'-triphosphate (ATP) infusions useful against metastatic refractory cancers are in Phase I of human clinical trials. The two questions which are being answered by these trials are: 1) is it possible to achieve the degree of elevation of red blood cells, and blood plasma compartment pools of ATP after the administration of ATP to patients as was shown extensively in preclinical murine models, and 2) can the elevated ATP levels in the human host produce the spectrum of anticancer activities demonstrated in experimental animals (Rapaport, E. Mechanisms of anticancer activities of adenine nucleotides in tumor-bearing hosts. Ann. N.Y. Acad. Sci. 603:142-150 [1990]).

A variety of in vitro and in vivo studies have demonstrated several anticancer activities of extracellular (blood plasma compartment) pools of ATP as well as elevated hepatic and red blood cell pools of ATP. These activities are a) cytostatic and cytotoxic effects on the tumor; b) anti-cachexia effects and improvement of hepatic and renal functions; c) modulation of tumoral blood flow; d) antianaemia effects; e) antipain activities; f) improvement in motor functions, performance status; g) improvements in oxygen delivery to peripheral sites; h) enhancement of superoxide anion (O_2^-) production by phagocytic cells and i) significant antithrombotic effects in vivo. All of these anticancer activities observed either in experimental animals or in humans after the administration of ATP have been reviewed recently (Rapaport, E. Anticancer activities of adenine nucleotides in tumor-bearing hosts. Drug Development Research 28:428-431 [1993]).

The administration of ATP to tumor-bearing murine hosts was also shown to markedly inhibit host weight loss in a cachectic tumor model and, as importantly, the administration of ATP or other adenine nucleotides was shown to elevate extracellular, blood plasma compartment steady state levels (pools) of ATP. The inhibition of tumor growth and host weight loss were shown not to exhibit a cause and effect relationship in murine models. The cytolytic activity of extracellular ATP against tumor cells is now being proposed by five different groups as accounting for the activity of certain cytolytic T lymphocytes (Filippini, A., Taffs, R. E. and Sitkovsky, M. V. Extracellular ATP in T-lymphocyte activation: Possible role in effector functions. Proc. Natl. Acad. Sci. USA 87:8267-8271 [1990]; Di Virgilio, F., Pizzo, P., Zanovello, P., Bronte, V. and Collavo, E. Extracellular ATP as a possible mediator of cell-mediated cytotoxicity. Immunol. Today 11:274-277 [1990]; Zheng, L. M., Zychlincky, A., Liu, C. C., Ojcius, D. M. and Young, J. D. Extracellular ATP as a trigger for apoptosis or programmed cell death. J. Cell Biol. 112:279-288 [1991]; Steinberg, T. H. and Di Virgilio, F. Cell-mediated cytotoxicity: ATP as an effector and the role of target cells. Curr. Opinion Immunol. 3:71-75 [1991]; Correale, P., Tagliaferri, P., Procopio, A., Coppola, V., Caraglia, M., Celio, L. and Bianco, A. R. ATP is a lymphokine activated killer (LAK) cell cytotoxic factor against colon cancer cells in vitro. Proc. Am. Assoc. Cancer Res. 33:324 [1992]). These cytolytic T lymphocytes release ATP which is stored in their cellular granules, in response to the target cell interaction with a T cell receptor. The extracellular ATP released in the immediate vicinity of the target tumor cell is proposed to deliver the lethal hit. All of these groups demonstrated tumor cell killing by extracellular ATP in a variety of systems.

SUMMARY OF THE INVENTION

Contrary to previously approved therapies and therapies that are known to be under development, the present invention is aimed at the activation of a multitude and a broad spectrum of host functions without directly attacking the virus (HIV) itself. The expansion of organ, red blood cell (total blood) ATP pools and the elevation of extracellular blood plasma adenosine and ATP levels produces the following effects in patients afflicted with AIDS:

1. Improvements of T-cell proliferation and cytotoxicity.
2. Down-regulation of TNF-α and IL-6 synthesis.
3. Improvements in gut absorptive capacity and in the integrity of the intestinal mucosa.
4. Reversal of cachexia-wasting by expansions of organ ATP pools and its mediated inhibition of hypermetabolism.
5. Positive effects on organ function.
6. Cytoprotection during administration of high-dose cytotoxic antiviral agents.

All of these activities will translate into improvements in specific clinical parameters which will ultimately yield survival benefits.

The present invention discloses for the first time a method for treatment of HIV disease/AIDS by administration of adenine nucleotides or adenosine and inorganic phosphate to a human host.

The present invention discloses for the first time that host functions in HIV disease/AIDS can be significantly improved by affecting a broad spectrum of physiological activities, immune and non-immune, with elevated levels of the natural agonists adenosine and ATP.

In particular, the present invention is concerned with a method for treating Human Immunodeficiency Virus infection, and/or Human Immunodeficiency Virus disease, and/or Acquired Immunodeficiency Syndrome related complex, and/or Acquired Immunodeficiency Syndrome, and/or Acquired Immunodeficiency Syndrome with secondary infections, by administering to a human host in need thereof a member selected from the group consisting of: (a) a mixture of adenosine and/or inorganic phosphate; and (b) an adenine nucleotide wherein said adenine nucleotide containing adenosine moiety(ies) and phosphate moiety(ies) and under-

goes rapid degradation to adenosine and inorganic phosphate after administration to said host.

BEST AND VARIOUS MODES FOR CARRYING OUT INVENTION

It has been found pursuant to the present invention that a host infected with Human Immunodeficiency Virus and/or suffering from Human Immunodeficiency Virus disease an Acquired Immunodeficiency Syndrome related complex and/or Acquired Immunodeficiency Syndrome and/or acquired Immunodeficiency Syndrome with secondary infections can be treated by being administered a member selected from the group consisting of: (a) a mixture of adenosine and/or inorganic phosphate; and (b) an adenine nucleotide wherein said adenine nucleotide containing adenosine moiety(ies) and phosphate moiety(ies) and undergoes rapid degradation to adenosine and inorganic phosphate after administration to said host.

Examples of such materials are adenosine 5'-monophosphate (AMP), adenosine 5'-diphosphate (ADP), adenosine 5'triphosphate (ATP) and mixtures of adenosine and an inorganic phosphate.

Examples of inorganic phosphates are sodium phosphate, potassium phosphate and phosphoric acid. The pH of any solution employed containing the phosphate is usually adjusted, if necessary, to about 6.0 to about 7.5 by the addition of a base such as sodium hydroxide. Usually, at least about 1 equivalent of phosphate per adenosine is employed, and preferably about 1 to about 3. In addition, pharmaceutically acceptable salt, or metal complexes, or chelates, or liposomes or radio-nuclides of the above compounds can be used.

Preparations containing the above ingredients can be employed in a variety of conventional pharmaceutical preparations. These preparations can contain organic or inorganic material suitable for internal administration. The high solubility of AMP and/or ADP and/or ATP salts and/or adenosine and phosphate salts in isotonic aqueous solutions of sodium chloride enable administration of these agents in the form of injection or infusion of single or multiple doses. The injection or infusion can be intraperitoneal, intravenous, or intra-arterial. AMP and/or ADP and/or ATP and/or adenosine and phosphate salts are also suitable for oral, enteral, or topical application when employed with conventional organic or inorganic carrier substances.

The effective doses are in the range of about 0.1-100 mg/kg of body weight per 24 hours for oral or topical administration, and 0.01-10 mg/kg of body weight per 24 hours for injections. Intravenous, intraperitoneal, or intraarterial infusions of AMP and/or ADP and/or ATP and/or adenosine and phosphate salts in a suitable salt form is preferably administered at a rate of about 0.001-1 mg/kg of body weight per minute. The delivery of these agents can be performed using a variety of drug delivery systems including, but not limited to, pumps or liposomes.

The present invention is based on the presence of purine receptors, the adenosine receptors and the ATP receptors on a variety of cells that affect immune and organ functions in HIV disease/AIDS. The present invention discloses for the first time that host functions in HIV disease/AIDS can be significantly improved by affecting a broad spectrum of physiological activities, immune and non-immune, with elevated levels of the natural agonists adenosine and ATP. The effects of adenosine analogues on a variety of cells is well-established (for a review, see Williams, M. Purinergic drugs: opportunities in the 1990's. Drug Development Research 28:438-444 [1993]). Recently it has also been shown that adenosine analogues that are resistant to metabolic enzymatic activities in mammalian hosts can affect cellular activities and functions that are expected to be highly beneficial to patients with HIV disease/AIDS. Adenosine or ATP are totally unexpected to serve as effectors in these systems in mammalian hosts, because of their well-known metabolic lability which teaches away from the possibility of using them in order to improve immune and non-immune functions in HIV disease/AIDS. As an illustration of the patentability of the present invention, attention is directed to two critical recent reports in this art. The first report (Hofmann, B., Nishanian, P., Nguyen, T., Liu, M. and Fahey, J. L. Restoration of T-cell function by reduction of intracellular CAMP levels with adenosine analogues. AIDS 7:659-664 [1993]) demonstrates that the chemically stable adenosine analogue 2',5'-dideoxyadenosine (ddAdo) can reduce cyclic AMP levels and increase both the proliferative capacity of T-cells to recall antigens and T-cell cytotoxicity in HIV seropositive individuals (without AIDS). These functions are required to be improved for an HIV disease/AIDS treatment to be clinically viable. It is what is often referred to as immune reconstitution. No mention or hint is given in the above cited paper as to the potential use of adenosine itself or ATP for the same purposes. The second report (Parmely, M. J. et al. Adenosine and a related carbocyclic nucleoside analogue selectively inhibit tumor necrosis factor-α production and protect mice against endotoxin challenge. Journal of Immunology 151:389-396 [1993] deals with the use of adenosine and its synthetic analogue for inhibiting tumor necrosis factor-α (TNF-α) production from activated macrophages. The requirement for reducing TNF-α and other cytokine levels as part of a successful treatment of HIV disease/AIDS has been established since these cytokines activate immune cells and have a significant stimulating (up-regulation) effect on HIV replication (Poli, G. et al. Tumor necrosis factor α functions in an autocrine manner in the induction of human immunodeficiency virus expression. Proc. Natl. Acad. Sci. USA 87:782-785 [1990]). Although it is stated that adenosine inhibited TNF-α production by activated mouse peritoneal macrophages, adenosine had no effect on RNA levels for TNF-α and most importantly "ADO failed to protect animals against endotoxin lethality, most likely due to the rapid metabolism of the nucleoside in vivo" (bottom of the abstract section). The conclusion to this report (Parmely et al., supra) demonstrates the patentability of the present invention. It states (end of abstract section) that "These results establish ADO and MDL201112 as potent inhibitors of TNF-α biosynthesis and suggest that MDL201112 or similar analogues warrant further study as potential agents for the treatment of endotoxin shock and other diseases in which TNF-α plays an important pathogenic role". Thus, adenosine (and even more so ATP) are totally discounted as potential drugs for HIV disease/AIDS due to their metabolic lability and the widely held notion that neither adenosine nor ATP can be utilized in vivo in a host. The methods disclosed in the present invention provide the art for elevating cellular ATP pools and extracellular adenosine and ATP levels for favorably affecting a wide spectrum of cellular and physiological functions required for the successful treatment of HIV disease/AIDS in human patients.

A variety of unrelated observations as will be discussed below in conjunction with my years of experience with adenine nucleotides and/or mixtures of adenosine and inorganic phosphates has lead me to now suggest the use of the above ingredients for the treatment of Human Immunodeficiency Virus infection, and/or Human Immunodeficiency Virus disease, and/or Acquired Immunodeficiency Syndrome

related complex, and/or Acquired Immunodeficiency Syndrome, and/or Acquired Immunodeficiency Syndrome with secondary infections.

Reversal of Cachexia-HIV Wasting Syndrome and Improvement of Organ Function

Mechanisms which were established by the effects of ATP administration to cachectic tumor-bearing murine hosts were recently applied to the treatment of advanced (stage III B and IV) non-small cell lung cancer and other advanced refractory cancers. It is important to note that benefits observed after ATP administration were obtained in spite of the less than favorable schedule of infusions, due to the Phase I nature of the trials, with the questions being addressed dealing mostly with tolerated doses, toxicities, adverse effects, pharmacokinetics and pharmacodynamics. The schedules consisted of continuous 48-96 hour infusions of ATP every fifth week. A doubling in total blood levels of ATP (red blood cell ATP pools) was observed in most patients after 48 hours of infusion (increases from basal levels of 0.9-1 mM to 1.6-2 mM of total blood ATP levels). As was predicted by the murine studies, total blood ATP levels declined over a period of several days after the termination of ATP infusions.

The protocols employed in the present invention as discussed above include infusions of adenine nucleotides or adenosine at levels of 0.001-1.0 milligram per kilogram of body weight per minute, injections of adenine nucleotides or adenosine in amounts of 0.01-10 milligrams per kilogram of body weight per 24 hours, or oral or topical administration of adenine nucleotides or adenosine in amounts of 0.1-100 milligrams per kilogram of body weight per 24 hours. It is beneficial that the levels of ATP or other adenine nucleotides or adenosine should not affect heart rate or mean arterial blood pressure but should produce reductions in systemic vascular resistance and pulmonary vascular resistance with small increases in cardiac output. Hyperuricemia is noticed in infusions that proceed for longer periods than 48 hours, and can be easily prevented by prophylactic use of allopurinol.

Extensive preclinical data suggest that the benefits observed in the initial Phase I trial are a result of the increases in organ and blood ATP levels after the administration of ATP. The most relevant to advanced AIDS are the increases in liver, kidney, splenocytes and gut ATP levels, which in experimental animals have been directly linked to marked improvements in these organs' functions. Several of the improvements related to the increases in red blood cell ATP levels will also contribute to the amelioration of cachexia and positive effects on quality of life parameters in patients suffering advanced HIV infections. These include anti-anaemia effects and improvements in oxygen delivery to peripheral sites. This latter increase in P_{O_2} at 50% O_2 saturation ("P_{50}, st") is a result of the increases in red blood cell ATP levels which in turn produce significant increases in the erythrocyte 2,3-diphosphoglycerate (DPG) and resulting in a decreased affinity between hemoglobin (Hb) and oxygen, increased tissue oxygen supply because of the facilitated unloading of oxygen from hemoglobin and the final result being an improvement in physical activity.

The ability of infused ATP to restore gut absorptive capacity is extremely significant in regard to the proposed treatment of advanced AIDS with ATP. Since malnutrition is commonly associated with advanced AIDS, total parenteral nutrition is commonly utilized by AIDS patients. Therefore, the ability of intravenously, intramuscularly, or orally administered ATP or other adenine nucleotides or adenosine to rapidly improve gut absorptive capacity and thus favorably affect oral food intake, or to prevent the changes that occur in the intestinal mucosa by improving organ function due to restoration of cellular ATP levels, is expected to have a significant impact on survival of patients with advanced AIDS. The beneficial effects on overall survival of advanced AIDS patients will be augmented by the highly positive effects of ATP expansions on liver and kidney functions.

Downregulation of Cytokines.

The activation of cytokines was demonstrated to have an up-regulatory effect on HIV replication. Cytokines were also shown to become elevated during HIV infections in vitro (Poli, G. et al. Tumor necrosis factor α functions in an autocrine manner in the induction of human immunodeficiency virus expression. Proc. Natl. Acad. Sci. USA 87:782-785 [1990]) or in vivo (Breen, E. C. et al. Infection with HIV is associated with elevated IL-6 levels and production. J. Immunol. 144:480-484 [1990]; Birx, D. L., Redfield, R. R., Tencer, K., Fowler, A., Burke, D. S. and Tosato, G. Induction of interleukin-6 during human immunodeficiency virus infection. Blood 76:2303-2310 [1990]). Whereas TNF-α was shown to possess a direct inductive effect on HIV replication in infected cells, interleukin 6 (IL-6) acts in the activation of B cells in HIV infected individuals. The ability of extracellular adenosine and ATP to reduce cellular synthesis and release of cytokines by monocytes and macrophages is dependent on the presence of membrane adenosine and ATP receptors.

The increase in intestinal blood flow and gut function after administration of adenine nucleotides or adenosine is also expected to contribute to an overall reduction in the levels of circulating cytokines in malnourished advanced AIDS patients, the reason being that those increases in intestinal blood flow and gut function are expected to bring about a repair of the mucosal erosions and reductions in submucosal edemas after administration of adenine nucleotides or adenosine. The improved integrity of the gut mucosa would prevent the low levels of translocation of bacteria and bacterial fragments through the mucosa and their subsequent powerful induction of cytokine synthesis and release.

Improvements in Immune Functions.

The improvements in immune functions by administration of adenine nucleotides or adenosine are of two types: the beneficial effects to the immune system generated by the improvements in organ functions, especially organs which directly affect the immune system such as improvements in liver, kidney, and splenic functions resulting in increased splenocyte IL-2 and IL-3 synthesis; and the recently identified restoration of T-cell function in HIV infection by adenosine which was linked to the adenosine analogues induced reduction in intracellular cAMP levels (Hoffmann, B., Nishinian, P., Nguyen, T., Liu, M. and Fahey, J. L. Restoration of T-cell function in HIV infection by reduction of intracellular cAMP levels with adenosine analogues. AIDS 7:659-664 [1993]). The ability of the administered adenine nucleotides to improve these functions is dependent on the unexpected finding that adenine nucleotides can expand liver, red blood cell and blood plasma (extracellular) ATP pools. The persistent catabolism or enzymatic degradation of the extracellular ATP to adenosine yields elevated extracellular adenosine levels sufficient to activate immune cell purine receptors, and improve immune function. Thus, the common notion that adenosine and ATP are too labile in vivo and only synthetic, chemically and enzymatically stable adenosine or ATP agonists can be utilized for the purpose of immune activation in vivo does not hold in light of the present invention.

The ability of elevated cyclic AMP levels to decrease proliferation and cytotoxicity in normal T-cells has been recog-

nized (Lingk, D. S., Chan, M. A. and Gelfand, E. W. Increased cAMP levels block progression but not initiation of human T-cell proliferation. J. Immunol. 145:449-455 [1990]). Increased cAMP levels were shown to exist in HIV infected peripheral blood mononuclear cells (PBMC) both in vitro after infection of normal PBMC with HIV and in vivo in T-cells isolated from HIV-seropositive individuals (Hoffmann, B., Nishinian, P., Nguyen, T., Liu, M. and Fahey, J. L. Restoration of T-cell function in HIV infection by reduction of intracellular cAMP levels with adenosine analogues. AIDS 7:659-664 [1993]). The mechanisms responsible for the significant inhibitory effects of elevated cAMP on T-cell proliferation and functions are linked to the activity of cAMP-dependent protein kinase (protein kinase A or PKA), which is high in cells from HIV-seropositive subjects. These data therefore suggest to me a mechanism for the decreased function of non-infected T-cells in HIV-seropositive subjects, since less than 1% of CD4 T-cells harbor HIV, yet the significant increases in cAMP levels are observed in cells from HIV-seropositive subjects without AIDS where the majority of the cells are not HIV-infected. Suggested herein as an explanation is immune activation of non-infected cells. The most important aspect of these studies is the ability to restore function by lowering cAMP with adenosine analogues. These analogues are synthetic, chemically and enzymatically stable derivatives of adenosine such as 2',5'-dideoxyadenosine, but not adenosine or ATP themselves.

Protection of Organ Function by Expanded ATP Pools would Enable the Administration of High Doses of Cytotoxic Antiviral Drugs.

Although current clinical utilization of antiviral nucleoside therapy such as zidovudine (AZT) is not associated with severe anaemia and severe hepatotoxicity that would render its use prohibitive in asymptomatic HIV infection, hematologic as well as hepatic toxic effects are observed to some extent, especially with high doses of zidovudine (Volberding, P. A. et al. Zidovudine in asymptomatic human immunodeficiency virus infection. N. Engl. J. Med. 322: 941-949 [1990]). However, the earlier trials of AZT that included subjects with advanced AIDS who were anemic before the initiation of therapy and whose nutritional status was poor demonstrated significant hematological toxicities attributed to AZT (Richman, D. D. et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N. Engl. J. Med. 317:192-197 [1987]). Serious anaemia or neutropenia during AZT treatment of advanced AIDS patients was significant, although AZT did not seem to severely affect hepatic, renal, or gastrointestinal absorptive functions in a large fraction of advanced AIDS patients. The present and future development of cytotoxic anti-HIV therapies (Johnston, M. I. and Hoth, D. F. Present status and future prospects for HIV therapeutics. Science 260:1286-1293 [1993]) which are likely to lead to adverse hepatic, renal, or gastrointestinal absorptive functions provide the incentive for the development of ATP as a protective agent. As discussed hereinabove, the demonstrated ability of administered ATP to act in expanding organ and total blood ATP pools is responsible for the improved organ and red blood cell functions. Function is directly related to ATP levels during adverse conditions, and extracellularly administered ATP acts by interacting with cell membrane P_2-purine receptors in stimulating, through an extracellular signal, cellular purine nucleotide synthesis as well as providing a salvage precursor, adenosine, for this synthesis.

The data discussed above lead me to assert the following conclusions: administration of adenine nucleotides or adenosine and inorganic phosphate to a patient suffering from HIV disease/AIDS will result in significant increases in organ and red blood cell ATP pools and as a result of the expanded red blood cell ATP pools, elevated levels of ATP and its catabolic product adenosine will be produced in the extracellular blood plasma compartment. These elevated extracellular ATP and adenosine levels are produced due to the release of micromolar amounts of ATP from red blood cells into the blood plasma in a non-hemolytic process and the constant degradation of ATP to adenosine by enzymatic activities present in the vascular bed. The therapeutic targets that will be achieved by the present invention for the treatment of HIV disease/AIDS are reversal of cachexia, improvements in performance status and organ function, down-regulation (inhibition of synthesis and/or release) of cytokines, improvements in immune cell function (immune reconstitution), and—due to the noted cytoprotection achieved by expansions of cell and organ ATP pools—combination of administration of adenine nucleotides or adenosine and inorganic phosphate along with or followed by antiviral cytotoxic drugs.

Having thus described my invention, what I claim as new and desire to secure by Letters Patent is:

1. A method for suppressing cachexia-wasting, and/or improving skeletal muscle functions, and/or slowing cancer progression by administering to a human host in need thereof a member selected from the group consisting of: (a) adenosine 5'-monophosphate; (b) adenosine 5'-diphosphate; (c) adenosine 5'-triphosphate; and mixtures thereof, pharmaceutically acceptable salt thereof, or chelate thereof, or metal complex thereof, or liposome thereof.

2. The method of claim **1** wherein said member is administered to a human host as pharmaceutically acceptable salt thereof, or chelate thereof, or metal complex thereof, or liposome thereof.

3. The method of claim **1** wherein adenosine 5'-monophosphate is administered to said host.

4. The method of claim **1** wherein adenosine 5'-triphosphate is administered to said host.

5. The method of claim **1** wherein skeletal muscle functions are improved in a human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

6. The method of claim **1** wherein cachexia-wasting is treated in a human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

7. The method of claim **1** wherein cancer progression is slowed in a human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

8. The method of claim **1** wherein the amount of adenosine 5'-monophosphate, and/or adenosine 5'-diphosphate, and/or adenosine 5'-triphosphate; is about 0.001-1 mg/kg of body weight per minute and said administering is by infusion.

9. The method of claim **1** wherein the amount of adenosine 5'-monophosphate; and/or adenosine 5'-diphosphate; and/or adenosine 5'-triphosphate is about 0.01-10 mg/kg of body weight per 24 hours and said administering is by injection.

10. The method of claim **1** wherein the amount of adenosine 5'-monophosphate; and/or adenosine 5'-diphosphate; and/or adenosine 5'-triphosphate; is about 0.1-100 mg/kg of body weight per 24 hours and said administering is oral or topical.

11. A method for suppressing cachexia-wasting, and/or improving skeletal muscle functions by administering to a human host suffering from HIV Disease a member selected from the group consisting of: (a) adenosine 5'-monophosphate; (b) adenosine 5'-diphosphate; (c) adenosine 5'-triph-

osphate; and mixtures thereof, pharmaceutically acceptable salt thereof, or chelate thereof, or metal complex thereof, or liposome thereof.

12. The method of claim **11** wherein said member is administered to a human host as pharmaceutically acceptable salt thereof, or chelate thereof, or metal complex thereof, or liposome thereof.

13. The method of claim **11** wherein adenosine 5'-monophosphate is administered to said host.

14. The method of claim **11** wherein adenosine 5'-triphosphate is administered to said host.

15. The method of claim **11** wherein skeletal muscle functions are improved in a human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

16. The method of claim **11** wherein cachexia-wasting is treated in said human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

17. The method of claim **11** wherein cancer progression is slowed in a human host by administering to said host adenosine 5'-monophosphate, and/or adenosine 5'-triphosphate.

18. The method of claim **11** wherein the amount of adenosine 5'-monophosphate; and/or adenosine 5'-diphosphate; and/or adenosine 5'-triphosphate; is about 0.001-1 mg/kg of body weight per minute and said administering is by infusion.

19. The method of claim **11** wherein the amount of adenosine 5'-monophosphate; and/or adenosine 5'-diphosphate; and/or adenosine 5'-triphosphate; is about 0.01-10 mg/kg of body weight per 24 hours and said administering is by injection.

20. The method of claim **11** wherein the amount of adenosine 5'-monophosphate; and/or adenosine 5'-diphosphate; and/or adenosine 5'-triphosphate; is about 0.1-100 mg/kg of body weight per 24 hours and said administering is oral or topical.

21. The method of claim **1** wherein said administering provides for suppressing cachexia-wasting, and/or improving skeletal muscle functions, and/or slowing the progression of cancer.

22. The method of claim **11** wherein said administering provides for suppressing cachexia-wasting, and/or improving skeletal muscle functions, and/or slowing the progression of cancer.

* * * * *

EXHIBIT C

PEAK ATP®
LICENSE AND SUPPLY AGREEMENT

THIS AGREEMENT is made and entered into this 9th day of January, 2009, by and between TSI Health Sciences, Inc., with offices at 7168 Expressway, Missoula, Montana 59808-8587 ("TSI"), and Golden State natural Products, with offices at3052 Industry St., Ste. 102, Oceanside, CA 92054 ("Licensee").

TSI has acquired, developed, licensed, and/or otherwise owns all right, title and interest in and to certain technology, inventions, trademarks, and know-how relating to Ingredient (defined below). Licensee desires to market and sell dietary supplements containing Ingredient purchased from TSI. TSI is willing to supply Ingredient to Licensee and to grant a license to practice and utilize TSI's technology, inventions, trademarks, and know-how, consistent with the terms and conditions set forth in this agreement.

In consideration of the mutual covenants and promises contained herein, and for other good and valuable consideration, TSI and Licensee agree as follows:

1: DEFINITIONS:

The following terms, when used with initial capitals in this Agreement, shall have the meanings given below:

1.1 "Letters Patent," as used in this Agreement, shall include United States patents and any and all patents issuing on patent applications enumerated at Appendix A, and any continuations, continuation-in-part, divisions, patents of addition, reissues or extensions of such patents or patent applications that are owned or licensed by TSI and which TSI has the right to grant licenses thereon to Licensee during the term of this Agreement.

1.2 "Ingredient" shall include adenosine 5'-triphosphate and adenosine 5'triphosphate disodium (herinafter "ATP" that is administered orally as a Dietary Supplement, resulting from the use of an Invention described and claimed in at least one claim of the Letters Patent.

1.3 "Products" shall mean any products containing Ingredient as identified in Appendix B, attached hereto.

1.4 "Dietary Supplement" shall mean those products that fall within the field generally recognized as dietary supplement, as that term is currently defined by U.S. regulatory bodies (Section 201 of the Dietary Supplement Health and Education Act of 1994 [DSHEA]) or in accordance with any narrower definition that U.S. regulatory bodies may adopt in the future.

1.5 "Efficacious Amount" shall mean 200-250 mg ATP disodium per day, divided in two (2) servings, on an empty stomach.

1.6 "Claim" shall mean a factual statement as to a biological property, function, feature, attribute, or characteristic of an ingredient.

1.7 "Licensed Field of Use" shall mean all Products that fall within the definition of U.S. Dietary Supplements, which specifically exclude drugs or pharmaceuticals requiring approval by the U.S. Food and Drug Administration or any respective foreign regulatory counterpart.

1.8 "Licensed Territory" shall mean the territory identified in Appendix B.

1.9 "Authorized Trade Channel" specify channels of trade from list in Appendix B.

1.10 "Licensed Materials" shall mean any research data, technical data, advertising, promotional and/or merchandising materials prepared and provided to Licensee by TSI.

1.11 "TSI Trademark" shall mean the mark "PEAK ATP" as a name, symbol, or design used to identify and distinguish Ingredient.

2. LICENSE GRANT:

Subject to the terms and conditions set forth in this Agreement, TSI hereby grants to Licensee a non-exclusive, non-transferable, royalty-free, revocable license to (a) use, sell, and otherwise commercialize Products in the Licensed Territory within the Licensed Field of Use and through the Authorized Trade Channel and (b) reproduce and use the TSI Trademark and the Licensed Materials in connection with the marketing, promotion, advertising, and sale or other distribution of Product.

3. PROPER USE OF TSI TRADEMARK:

3.1 Usage: Licensee covenants to use the TSI Trademark on all labels, packaging, advertising, and promotional materials for Products and not to use the TSI Trademark on any product that is not within the scope of the invention which is described and claimed in the Letters Patent. In the event TSI changes or adopts another trademark, Licensee will be given a period of six (6) months to sell any inventory of Products bearing the old mark.

3.2 Review: Prior to use, Licensee shall provide TSI with samples of all labels, advertisements, brochures, literature, packaging materials and the like prepared by or for Licensee, which display the TSI Trademark. TSI agrees to promptly review such samples and promptly communicate approval or disapproval of such samples. If samples are disapproved, Licensee agrees to modify the samples to bring them into conformity with TSI's specifications prior to use. If Licensee does not receive written disapproval within three (3) days of receipt of Licensee's submission of the samples to TSI, approval shall be deemed granted.

3.3 Ownership Notation: Licensee agrees that each and every label, package, display, advertisement, and piece of promotional material must attribute ownership of the TSI Trademark and the associated goodwill to TSI by using the ® symbol and by using the following trademark attribution -- "PEAK ATP® is a registered trademark of TSI Health Sciences, Inc.

3.4 Ownership: Licensee shall not adopt, use, or register any words, phrases or symbols which are identical to or confusingly similar to the TSI Trademark and shall not use the TSI Trademark as part of its corporate or trade name or permit any third party to do so.

4. BRANDING OF LICENSED PRODUCT:

4.1 Formulation: Licensee agrees to only use Ingredient in Dietary Supplements and in delivery forms agreed to in advance by TSI. TSI reserves the right to reject the inclusion of its Ingredient in a Product if it is reasonable believed that the Ingredient may not be efficacious in the Product and/or the delivery form proposed by Licensee.

4.2 Marking: Licensee agrees to mark the Product or the advertising and marketing materials associated therewith, with the respective number of each of such Letters Patent and/or with notice of "patent pending" status.

4.3 Licensed Materials: Licensee may use the Licensed Materials in advertising and marketing the Products only in accordance with the instructions provided by TSI. Licensee shall make no use of the Licensed Materials other than that expressly approved by TSI in advance and Licensee shall not modify or alter any of the Licensed Materials in any way unless expressly approved to in advance and in writing by TSI.

4.4 Inspection: Licensee agrees at all reasonable times, and with reasonable advance written notice, to permit TSI or TSI's duly authorized representatives to inspect the Products, either on the premises of Licensee or by written request of TSI that Licensee provide specimens of Licensed Products for off-site testing and/or analysis by TSI, with which the TSI Trademark is used or is intended to be used for the purpose of confirming safety, compatibility of actives, stability and efficacy of the Products.

5. REPRESENTATIONS AND WARRANTIES:

5.1 Authority to Enter Into Agreement: TSI and Licensee each represent and warrant to the other that it possesses all of the requisite power and authority to enter into this Agreement and to perform each and every term, provision, and obligation of this Agreement, and that neither the execution or delivery of this Agreement nor the performance of the terms of this Agreement will conflict with or result in a breach of the terms, provisions, or obligations of, or constitute a default under, any other agreement or instrument under which such party is obligated.

5.2 Ingredient Warranty: TSI warrants that it has good title to the Ingredient delivered and that the Ingredient is safe for human consumption when used in accordance with the dose limitations, warning, or other conditions that TSI may provide to Licensee; and that the Ingredient delivered to Licensee shall conform to product specifications provided by TSI attached as Addendum F. THESE ARE THE ONLY WARRANTIES GIVEN TO LICENSEE, AND ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, ARE EXCLUDED. In the event of a breach of warranty, TSI will replace the defective Ingredient but shall have no liability to Licensee and in no event shall TSI be liable for any incidental, consequential, or special damages arising out of any breach of warranty or breach of the terms of this Agreement.

6. CONFIDENTIAL DISCLOSURES:

6.1 Sharing of Confidential Information: As used in this Section 6 and elsewhere in this Agreement, the term "Confidential Information" shall include any technical or commercial information of any type given by TSI to Licensee, or to which Licensee obtains access under this Agreement, which in the evaluation of TSI is confidential, proprietary, or secret (whether or not in fact or law actually being confidential, proprietary or secret), provided that notice of said evaluation is communicated from TSI to Licensee at the time when the technical or commercial information is given to and/or obtained by Licensee.

6.2 Precautions: Licensee agrees that it will take reasonable precautions to preserve the confidential, proprietary, or secret status of any Confidential Information. Licensee shall require that its employees, contractors and agents, understand and agree to treat and to hold such Confidential Information in confidence consistent with the provisions herein.

6.3 Obligation of Confidence: The obligations of this Section 6 shall survive termination of this Agreement for a period of three (3) years; provided, however, that such obligations shall not apply to:

(a) any Confidential Information which Licensee can reasonably demonstrate was disclosed to Licensee by a third party that was at the time of that disclosure under no obligation of confidentiality to TSI or to any party in privity with TSI; or

(b) any Confidential Information which Licensee can reasonably demonstrate through documentation has at any time become generally known to the trade or public through no fault or action on the part of Licensee.

7. LETTERS PATENT AND IMPROVEMENTS:

7.1 TSI's Ownership Interest: TSI is and shall be the owner of all rights, title and interest in and to the following: (1) all original data or written materials originated and/or prepared for Licensee by TSI, including designs, plans, drawings, specifications, compositions, formulae, methods, systems, processes, techniques, research data and Know-How; (2) all ideas, concepts, know-how or techniques relating to such data or written materials developed during the course of this Agreement between the parties; and (3) all inventions, discoveries, works of authorship, or improvements, including products, concepts, ideas, techniques, methods, know-how, data, specimens and prototypes relating to the Ingredient that were (a) developed by TSI or (b) conceived or originated by TSI, during the course of this Agreement.

7.2 Licensee's Ownership Interest: Licensee is and shall be the owner of all rights, title and interest in and to all inventions, discoveries, works of authorship, or improvements, including products, concepts, ideas, techniques, methods, know-how, data, specimens and prototypes relating to Products containing ATP developed by Licensee or (b) conceived or originated by Licensee, during the course of this Agreement.

7.3 Joint Inventions: TSI and Licensee are and shall be the co-owners of all rights, title and interest in and to all inventions, discoveries, works of authorship, or improvements, including products, concepts, ideas, techniques, methods, know-how, data, specimens and prototypes relating to products containing ATP jointly developed by both Licensor and Licensee or (b) conceived or originated by both Licensor and Licensee, during the course of this Agreement.

7.4 Disclosure: TSI and Licensee covenant and agree that they will promptly communicate and disclose to the other party all such data, materials, ideas, concepts, know-how, techniques, inventions, discoveries, works of authorship, and improvements, whether patentable or copyrightable or not, referred to in paragraphs 7.1 and 7.2 above, together with any and all other enhancements, uses, modifications and/or improvements of or relating to the Ingredient or products containing ATP which TSI or Licensee conceive, work upon or otherwise become aware of during the term of this Agreement.

7.5 Cross-License: TSI and Licensee further agree to cross-license each such idea, concept, technique, invention, discovery, work of authorship, improvement, use, enhancement and modification developed during the course of this Agreement referred to in paragraphs 7.1 and 7.2 above, including without limitation a cross-license in and to any data, materials, know-how, patents, copyrights or trade secrets which embody all or any part thereof. Both TSI and Licensee agree to execute, acknowledge and deliver any and all instruments, documents and papers and to do any and all other things that may be deemed to be reasonably necessary by the parties to carry out the provisions of this Section 7.

8. COMPLIANCE WITH LOCAL LAWS/INDEMNITY:

Licensee agrees to fully comply, at its own expense, with all applicable laws and regulations relating to its sale of Products. TSI makes no representation regarding (i) the ability of Licensee to sell Products in the Licensed Territory within the Licensed Field of Use and through the Authorized Trade Channel, or (ii) any regulations or restrictions applicable to the sale of Product in the Licensed Territory within the Licensed Field of Use and through the Authorized Trade Channel. Licensee is solely responsible for compliance with all applicable laws and regulations and agrees to indemnify TSI from and against all claims, liabilities, loss, and damages, including reasonable attorney fees, incurred by TSI arising out of or in connection with Licensee's failure to comply with such laws and regulations.

9. PRICE AND ORDERING:

During the term of this Agreement, Licensee will pay TSI for Ingredient according to the Price Schedule set forth in Appendix C.

10. TERMINATION:

Either party may, by giving thirty (30) days written notice, terminate this Agreement and, except as provided below, the rights or obligations of the parties hereto shall terminate. Termination of this Agreement shall not release either party form the obligation to make payments of any amounts due or form any other liabilities accrued during the term of the Agreement, which obligations shall continue. Upon termination of this Agreement, the licenses granted in Section 2 shall terminate, except that if Licensee has not defaulted in its obligation, the licenses granted to Licensee shall continue for a period no longer than one hundred eighty (180) days after the effective date of termination solely to permit the sell-off of any residual inventory of Products. Neither party shall be entitled to, or claim that it is entitled to, any compensation or like payment as a result of or arising out of any termination of the Agreement in accordance with its terms, whether claimed as a loss of goodwill, lost profits, lost opportunity, or otherwise.

11. NO ENDORSEMENT:

Licensee acknowledges that TSI makes no claims on behalf of Licensee's company as to the quality of the Products Licensee offers for sale and, accordingly, Licensee shall make no claims that TSI endorses any of Licensee's Products.

12. ENTIRE AGREEMENT:

This Agreement, which contains Appendices A-E, constitutes the entire agreement between the parties concerning the subject matter hereof and supercedes all proposals, oral or written, all negotiations, conversations, and/or discussions between the parties relating to this Agreement and all past course of dealing or industry customs. This Agreement may not be modified except in a writing signed by authorized representatives of both parties. This Agreement shall be deemed to have been entered into and shall be construed and enforced in accordance with the laws of the State of Utah. Nothing in this Agreement shall be construed as making either party the agent or representative of the other or creating a joint venture or partnership of the parties. Neither party is granted any right or authority to assume or to create any obligation or liability on behalf of or in the name of the other party.

IN WITNESS WHEREOF, the parties, by their duly authorized representatives, have caused this Agreement to be duly executed as of the date first mentioned above.

TSI Health Sciences, Inc.	Golden State Natural Products, Inc.
Signature	Signature
Larry Kolb	Brian Rubach
Printed Name	Printed Name
President	President
Title	Title
6-24-09	6/24/09
Date	Date

APPENDIX A

LETTERS PATENT

Patent No. Issue Date	Title Inventor(s)/Applicant(s)
United States	
U.S. Patent No. 6,723,737 Issued: April 20. 2004	METHODS, PHARMACEUITICAL AND THERAPEUTIC COMPOSITIONS FOR ADMINISTERING ADENOSINE Ellezer Rapaport
U.S. Patent No. 5,227,371 Issued: July 13, 1993	UTILIZATION OF ADENINE NUCLEOTIDES AND/OR ADENOSINE AND INORGANIC PHOSPHATE FOR ELEVATION OF LIVER, BLOOD AND BLOOD PLASMA ADENOSINE 5'-TRIPHOSPHATE CONCENTRATIONS Eliezer Rapaport
U.S. Patent No. 5,049,372 Issued: September 17, 1991	ANTICANCER ACTIVITIES IN A HOST BY INCREASING BLOOD AND PLASMA ADENOSINE 5'-TRIPHOSPHATE (ATP) Eliezer Rapaport
U.S. Pat. App. Serial No. 10/162,143 Filing Date: June 3, 2002 Priority Date: June 4, 2001	METHOD FOR INCREASING HUMAN PERFORMANCE BY REDUCING MUSCLE FATIGUE AND RECOVERY TIME THROUGH ORAL ADMINISTRATION OF ADENOSINE TRIPHOSPHATE Steve S. Lee et al

APPENDIX B

AUTHORIZED DISTRIBUTION

Please confirm one or more

Product:
Enteric Coated Tablets _____

Orally dissolving tablets _____

Beverage Mixes ✓

RTD Beverages ✓

Other (Please specify) Liquid Dietary Supplements

Licensed Field of Use:
U.S. Dietary Supplements ✓

Other (Please specify) _____

Licensed Territory:
USA and all its territories ✓

Other (Please specify) ✓ Global internet

Potential Trade Channels: Initial each trade channel you wish to participate in

Direct Consumer Sales (Internet / Mail Order Catalog) ✓

Specialty Market (Health Food) ✓

Multi-Level-Marketing _____

Mass Market ✓

Membership Clubs ✓

Other Gyms, Health Food outlets Bonnington's etc.

APPENDIX C

PRICE SCHEDULE

ATP002 PEAK ATP® Adenosine 5'-Triphosphate Disodium 430.00 ~~$525.00~~/kg

TSI and Licensee agree that in the event the Chinese and U.S. currency exchange radically changes or that in the event of a fluctuation in the value of Chinese currency, the price for PEAK ATP will automatically be adjusted to reflect the change or fluctuation so long as the currency change is greater than five percent (5%). The Wall Street Journal Currency chart will provide the basis for determining the extent of fluctuation or change in the Chinese currency exchange rate respective to the U.S. Dollar. The price shall also be adjusted in the event of a change in the Value Added Tax Rebate given by the Chinese government for exporters. The price change based upon the rebate change shall be effective at the time of the rebate change.

APPENDIX D

INGREDIENT SPECIFICATION

TSI HEALTH SCIENCES

SPECIFICATION

ATP002 • 8/25/06 • Rev 4

PEAK ATP

Adenosine 5'-Triphosphate Disodium

	Determination	Specification	Method
Physical Properties	Appearance	White to off white powder	Organoleptic
	Particle Size	NLT 80% through USS #80 (180 micron)	Ro Tap
Analytical	ATP Disodium ($C_{10}H_{14}N_5Na_2O_{13}P_3$)	NLT 96.0% (adb)	HPLC
	UV Absorption	λ max. = 257±1 nm	UV
		A_{250}/A_{257} = 0.79 to 0.89	
		A_{240}/A_{257} = 0.17 to 0.27	
	Sodium (Na)	NMT 8% (adb)	AA
	pH (1%)	2.4 - 4.5	USP
	Loss on Drying	6.0-12.0%	USP
	Residual Solvents	NMT 0.1%	GC
	Related Compounds (AMP, ADP)	NMT 4%	HPLC
	Heavy Metals	NMT 20 ppm	USP
	Arsenic (As)	NMT 1 ppm	USP
	Iron (Fe)	NMT 1000 ppm	USP
Microbial	Total Aerobic	NMT 100 cfu/g	USP
	Yeast & Mold	NMT 100 cfu/g	USP
	E. coli	Negative	USP
	Salmonella	Negative	USP
Other	Shelf Life	When the product is stored in unopened drums under optimal conditions, the shelf life of this product should exceed two years from the date of manufacture.	
	Shipping Information	Available in 10 kg double poly-lined fiber drums	

www.tsihs.com

7168 Expressway . Missoula, MT 59808-9537 . (406) 549-9123 . (406) 549-6139 fax . (877) 549-9123 toll free

EXHIBIT D

DAVISBROWN LAW FIRM

REPLY TO DES MOINES OFFICE

December 13, 2012

VIA CERTIFIED MAIL
Brian Rubach
Golden State Natural Products, Inc.
2080 Las Palmas Dr., Suite 103
Carlsbad, CA 92011

Re: Infringement of United States Patents Covering Adenosine Triphosphate

Dear Mr. Rubach:

We represent TSI, Inc. ("TSI") of Missoula, Montana in matters related to intellectual property. TSI is the owner of United States Patent No. 7,629,329 ("the '329 patent) entitled "Method for Increasing Muscle Mass and Strength Through Administration of Adenosine Triphosphate." TSI also is the owner, through a license agreement, of patent rights under United States Patent No. 7,671,038, also related to uses of adenosine triphosphate ("ATP").

It has come to our attention that you are offering ATP for sale in the United States. Please be advised that your use of ATP, in the absence of a license from TSI, infringes at least one of the patents described above.

TSI has devoted considerable time, effort, and expense in the development and marketing of ATP, and for this reason vigorously enforces its intellectual property rights. We insist that you immediately cease and desist from making, using, selling, or offering for sale any ATP or ATP-containing products. Additionally, please provide us documentation reflecting the following:

1. A summary of the amount of ATP product purchased or manufactured by Golden State Natural Products over time; the dates of those purchases or productions; the identity of your source of that material; and the amount you paid for it;

PHONE 515.288.2500 FIRM FAX 515.243.0654 WEB WWW.DAVISBROWNLAW.COM
THE DAVIS BROWN TOWER
215 10TH STREET, STE. 1300
DES MOINES, IA 50309
THE HIGHLAND BUILDING
4201 WESTOWN PKWY, STE. 300
WEST DES MOINES, IA 50266

2. A summary of the amount of ATP product sold by Golden State Natural Products over time; and the amounts received in consideration for them; and

3. The amount of ATP inventory Golden State Natural Products currently has on hand.

This information is necessary to determine the scope of your infringement and to evaluate what additional corrective steps may be required.

Please confirm for use by **December 27, 2012** that any such making, using, selling, or offering for sale of ATP or ATP-containing products has ceased and will not resume while the above-listed patents are in force. We also need the information requested by this correspondence at your earliest convenience, but in no event later than **December 27, 2012**.

We sincerely hope that this notice brings an end to your infringement and that provision to us of the requested information will allow us to resolve this matter on an amicable basis. We must point out, however, that failure on your part to timely provide us with the requested assurances and information will require further legal action. TSI will protect its intellectual property rights to the fullest extent of the law if necessary. We also wish to remind you that among the remedies for willful patent infringement are attorney's fees and treble damages.

We expect your immediate attention to this matter.

Sincerely,

DAVIS, BROWN, KOEHN, SHORS & ROBERTS, P.C.

Emily Harris

Emily E. Harris

cc: Larry Kolb

EXHIBIT E

LAW OFFICE OF RICHARD CLEGG
501 WEST BROADWAY, SUITE 800
SAN DIEGO, CA 92101

619-400-4924 (main)
619-400-4925 (direct)

www.richardclegglaw.com
rick@rclegglaw.com

December 27, 2012

Ms. Emily Harris
Davis, Brown, Koehn, Shors & Roberts, P.C.
215 10th Street
Suite 1300
Des Moines, IA 50309

Re: Your December 13, 2012, letter to Golden State Natural Products, Inc.

Dear Ms. Harris,

I represent Golden State Natural Products, Inc. ("GSNP") regarding intellectual property matters. GSNP has asked me to respond to the letter you sent to it on December 13, 2012, on behalf of your client TSI, Inc.

Your letter accused GSNP of infringing two separate patents. The first patent is U.S. Patent No. 7,629,329, entitled "Method for increasing muscle mass and strength through administration of adenosine triphosphate" ("the '329 Patent"). The second patent is U.S. Patent No. 7,671,038, entitled "Method of therapeutic treatments including human immunodeficiency virus (HIV) disease and other conditions in a human host by administering adenine nucleotides" ("the '038 Patent"). Contrary to what the "Re" line of your letter suggests, neither of the two patents covers adenosine triphosphate (ATP). Rather, both patents cover specific methods that involve the use of ATP.

As its title suggests, the claims of the '329 Patent are all directed to methods for increasing muscle strength (claim 1) or muscle mass (claim 11) in a mammal by administering an effective amount of Adenosine Triphosphate ("ATP") to the mammal while the mammal is participating in a strength training program.

Simply put, GSNP has not performed any such method, so it has not directly infringed the patent.

Nor has GSNP infringed the '329 Patent indirectly, through contributory infringement or inducement of infringement. ATP is a staple item of commerce, so, under 35 U.S.C. §271(c), GSNP could not be liable as a contributory infringer of the '329 Patent just for selling ATP, even if its customers for ATP (or their customers) are somehow using the product in a manner that could be considered a direct infringement of the '329 Patent. GSNP also cannot be liable for inducing any direct infringements by others, because it has not instructed or induced anyone to use the ATP in any particular way. Further, as I assume you are aware, to be liable as an inducer of another party's direct infringement, GSNP must have known about the patent and must have actually intended for the other party to infringe the patent. *DSU Medical Corp. v. JMS Co. Ltd.*, 471 F.3d 1293 (Fed. Cir. 2006). GSNP has had no such knowledge or intent.

With respect to the '038 Patent, you assert that TSI is the "owner" of rights in the patent "through a license agreement," but you do not say whether the license agreement is exclusive, non-exclusive or otherwise. As an initial matter, if TSI is not an exclusive licensee under the '038 Patent, it would not have any right to assert the '038 Patent against anyone.

Regardless, the fact remains that the '038 Patent is limited to a very specific method for treating very specific physical ailments, by "administering to a human host in need thereof a member selected from the group consisting of: (a) adenosine 5'-monophosphate; (b) adenosine 5'-diphosphate; (c) adenosine 5'-triphosphate; and mixtures thereof, pharmaceutically acceptable salt thereof, or chelate thereof, or metal complex thereof, or liposome thereof."

As with the '392 Patent, GSNP has not administered ATP to anyone, for any reason. It has not performed any method claimed in the '038 Patent, so it has not directly infringed the patent.

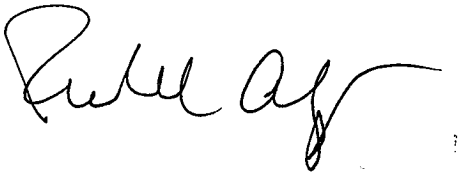
Nor has it infringed the '038 Patent indirectly, through contributory infringement or inducement of infringement. Again, ATP is a staple item of commerce, so GSNP could not be liable as a contributory infringer of the '038 Patent just for selling ATP, even if its customers for ATP (or their customers) are somehow using the product in a manner that could be considered a direct infringement of the '038 Patent. GSNP also cannot be liable for inducing any direct infringements by others, because it has not instructed or induced anyone to use its ATP in a particular way, was not previously aware of the '038 Patent and has not intended for any other party to infringe the patent.

In short, your accusations against GSNP are objectively baseless. If you have any actual evidence to support any of your accusations, please disclose it to

us. Otherwise, GSNP has no intention of complying with any of the demands you made in your letter, and will vigorously defend itself if your client files any court action to try to enforce either of the two patents against GSNP.

I look forward to receiving your response. If I do not hear back from you by January 15, 2013, we will assume that your client has dropped its accusations against GSNP.

Best regards,



Richard A. Clegg

RAC/njk

EXHIBIT F

DAVISBROWN LAW FIRM

REPLY TO DES MOINES OFFICE

February 5, 2013

VIA EMAIL: rick@rclegglaw.com
Mr. Richard A. Clegg
501 West Broadway, Suite 800
San Diego, CA 92101

Re: TSI, Inc./Golden State Natural Products, Inc. (GSNP)

Dear Mr. Clegg:

We have reviewed your December 27, 2012 letter and disagree with several points you have raised. It is particularly noteworthy that your letter makes no mention of the longstanding relationship between TSI and GSNP and the license agreement between the parties governing GSNP's use of ATP. TSI's records show that GSNP (1) has known about at least one of the patents since at least 2009 and (2) GSNP had the requisite specific intent to induce infringement.

TSI's records reflect the following regarding GSNP:

- GSNP began ordering ATP from TSI in 2008.
- In 2009, Brian Rubach of GSNP executed a license agreement with TSI covering GSNP's use of ATP.
- Patent application serial number 10/162,143, which later issued as the '329 patent, was part of this license agreement. The license agreement required GSNP to exclusively use TSI's ATP in its products.
- In 2010, Mr. Rauch informed TSI that his ATP customer was itself not willing to sign a license agreement, but did acknowledge his understanding via email that only TSI's ATP could be used in the products it was making.

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THE HIGHLAND BUILDING
4201 WESTOWN PKWY, STE. 300
WEST DES MOINES, IA 50266

THE AMES OFFICE
2605 NORTHRIDGE PKWY
AMES, IA 50010

- In 2011, TSI was informed that GSNP's customer was Apex Energetics and that the products containing ATP were dietary supplements, namely Nitric Balance K-62 and Nitric Balance K-68 and GSNP purchased approximately 163kg during 2011.

- GSNP purchased no ATP from TSI during 2012. In October 2012, GSNP informed TSI that it was still including ATP in products (and we assume those products to be Apex Energetic's supplements) but was obtaining ATP from another source.

Patent Infringement

TSI believes that GSNP has knowingly induced infringement of the '038 and '329 patents. These patents cover methods of use of ATP and the claimed methods are performed when a consumer uses Apex Energetic's dietary supplements. GSNP was aware of TSI's patents covering use of ATP, knew that the products it was formulating infringe when used, yet knowingly and willfully made the product anyway.

Your assertions that GSNP had no knowledge of these patents are not accurate. GSNP knew about application serial number 10/162,143, which later became the '329 patent, in 2009 as it was part of the license agreement that it executed. In *Genetech v. Trustees of the University of Pennsylvania*, 871 F.Supp.2d 963 (N.D. Ca. 2012), the court found that knowledge of a pending patent application can meet the knowledge requirement that has been read into Section 271(b). Thus, GSNP is presumed to have knowledge of the '329 patent as early as 2009.

Further, even if GSNP was unaware of either patent, our December 13, 2012 letter notifying GSNP of these two patents and TSI's position on infringement then put GSNP on actual notice of these patents. Knowledge and the requisite specific intent to induce infringement may be shown if the accused party continues to induce infringement even after learning of the patents. See *Classen Immunotherapies, Inc. v. Biogen IDEC*, 2012 WL 1963412 (D. Md. 2012). Your letter indicates that GSNP intends to continue using ATP in its products even in view of our initial notice letter, which evidences their specific intent to infringe.

Turning to the requirement that the accused infringer have specific intent to induce infringement, we believe that GSNP clearly has the requisite intent. GSNP cannot pretend it doesn't know what products in which ATP is being used. GSNP knows the specific products that its customer (Apex Energetics) sells and cannot maintain that it doesn't know how the products are marketed to or used by the end user. This is obviously not an instance wherein only a small percentage of the ultimate end uses of the product infringe the claimed methods, nor does

GSNP lack knowledge of what the product is used for. Instead, GSNP knows that the Apex products are dietary supplements and that all end users of the product that GSNP prepares infringe the two patents.

Again, we believe that GSNP infringes, under Section 271(b) of the Patent Act, at least one claim of the '329 patent and/or the '038 patent. We demand that GSNP immediately cease and desist selling any and all products containing ATP.

Contract Issues

As indicated above, Mr. Rubach executed a license agreement in 2009 on behalf of GSNP. The license agreement terminates upon thirty days written notice to the other party. GSNP has never provided TSI the requisite written notice terminating the agreement. The agreement requires GSNP to use only TSI's ATP and in delivery forms agreed to in advance by TSI. GSNP stopped purchasing ATP from TSI at some point in 2011 and for the entirety of 2012, yet never provided written notice to TSI that it was terminating the agreement. In addition to liability for patent infringement, we believe that GSNP breached the license agreement and has been in breach of contract since it began purchasing ATP from any party other than TSI and is liable for those damages as well.

We expect a response to this letter no later than **February 19, 2013**. If GSNP does not comply with our demands, we will recommend to our client that they pursue judicial remedies.

Sincerely,

DAVIS, BROWN, KOEHN, SHORS & ROBERTS, P.C.

Emily E. Harris